45 Cancer of the Esophagus

Mitchell C. Posner, Bruce D. Minsky, and David H. Ilson

INTRODUCTION

Esophageal cancer is unique among the gastrointestinal tract malignancies because it embodies two distinct histopathologic types: squamous cell carcinoma and adenocarcinoma. Which type of cancer occurs in a given patient or predominates in a given geographic area depends on many variables, including individual lifestyle, socioeconomic pressures, and environmental factors. In recent decades, the United States, along with many other Western countries, has witnessed a profound increase in incidence rates of adenocarcinoma, whereas squamous cell carcinoma continues to predominate worldwide. Although it would seem appropriate to individualize treatment of these tumors, in the past, they have often been managed as a single entity. Although present-day therapeutic interventions have begun to have an impact, with statistically significant improvement in survival over the most recent 3 successive decades, cancer of the esophagus remains a highly lethal disease as evidenced by the case fatality rate of 90%. However, a more thorough understanding of the initiating events, the molecular biologic basis, and treatment successes and failures has begun to spawn a new era of therapy aimed at targeting both adenocarcinoma and squamous cell carcinoma of the esophagus.

EPIDEMIOLOGY

The epidemiology of esophageal cancer is defined by its substantial variability as a function of histologic type, geographic area, gender, race, and ethnic background.[1] Because of the recent increase in incidence rates of adenocarcinoma, especially in the Western hemisphere, epidemiologic studies are now distinguishing between histologic types when reporting results, whereas in the past, incidence rates of esophageal cancer reflected only squamous cell carcinoma. This remains true in high-incidence areas where published rates are not obtained from population-based tumor registries. These high-incidence areas include Turkey, northern Iran, southern republics of the former Soviet Union, and northern China, where incidence rates exceed 100 per 100,000 person-years. Incidence rates of squamous cell carcinoma may vary 200-fold between different populations in the same geographic area because of unique cultural practices. The highest incidence rates for males (more than 15 per 100,000 person-years) reported from population-based tumor registries were in Calvados, France; Hong Kong; and Miyagi, Japan; and the highest rates for females (more than 5 per 100,000 person-years) were in Bombay, India; Shanghai, China; and Scotland.[2]

Esophageal cancer is relatively uncommon in the United States, and the lifetime risk of being diagnosed with the disease remains less than 1%.[3] It was estimated that 17,990 new cases would be identified in 2013, with 15,210 patients expected to die of the disease.[4] Age-adjusted incidence rates are essentially equivalent among African American and Caucasian men (Fig. 45.1), although the predominant histologic type in African American men is squamous cell carcinoma. The incidence rates for African American men peaked in the early 1980s, and since then they have shown a marked decline to the current rate of approximately 7 per 100,000 person-years.[3] Incidence rates among Caucasian men increased up until the year 2000, reflecting the marked increase in the incidence of adenocarcinoma of the esophagus of more than 400% in the past 2 decades, but now have stabilized between 7 and 8 per 100,000 person-years.[3] Although the incidence of esophageal cancer in Caucasian females (1.6 per 100,000) is lower than that in Caucasian males, rates of adenocarcinoma have increased in women by more than 300% during the past 20 years. Similar trends have been noted in Western European countries. This trend of increased incidence of adenocarcinoma of the esophagus has paralleled the upward trend in rates of both gastroesophageal reflux disease and obesity.

A steady decline in esophageal cancer mortality has been noted since the mid-1980s in the non-Caucasian U.S. population, whereas a marked increase in mortality was noted among Caucasian men and women during the same period (Fig. 45.2).[3] The mortality rates among men are markedly higher than women, regardless of race. Although survival rates for all esophageal cancer patients are uniformly dismal, regardless of race or gender, 5-year relative survival rates have significantly improved since the 1970s (5% if diagnosed in 1975 to 1977 versus 19% if diagnosed in 2003 to 2009) based on Surveillance, Epidemiology, and End Results (SEER) population-based tumor registry reporting.[3] There is no survival difference related to cell type (squamous cell carcinoma versus adenocarcinoma).

ETIOLOGIC FACTORS AND PREDISPOSING CONDITIONS

Squamous cell carcinoma and adenocarcinoma of the esophagus share some risk factors, whereas other risk factors are specific to one histologic type or the other.

Tobacco and Alcohol Use

Tobacco and alcohol use are considered the major contributing factors in the development of esophageal cancer worldwide. It is estimated that up to 90% of the risk of squamous cell carcinoma of the esophagus in Western Europe and North America can be attributed to tobacco and alcohol use.[5] Population-based studies demonstrate that tobacco and alcohol use are independent risk factors, and their effects are multiplicative, as evidenced by the association of the highest risk of developing esophageal cancer with heavy use of both agents. Approximately 65% and 57% of squamous cell carcinomas of the esophagus have been attributed to smoking tobacco for longer than 6 months in Caucasian and African American men, respectively, in the United States.[6] There appears to be a dose–response effect related to the duration and intensity of smoking, and, importantly, there is an impressive (up to 50%) reduction in the risk of developing squamous cell carcinoma of the esophagus for those who quit smoking and an inverse relationship between risk and the length of time since cessation of

۰۲۱-۶۶۱۹۸۵۱۴ www.myuptodate.com tahir99 - UnitedVRG دریافت آخرین نسخه آپتودیت آفلاین

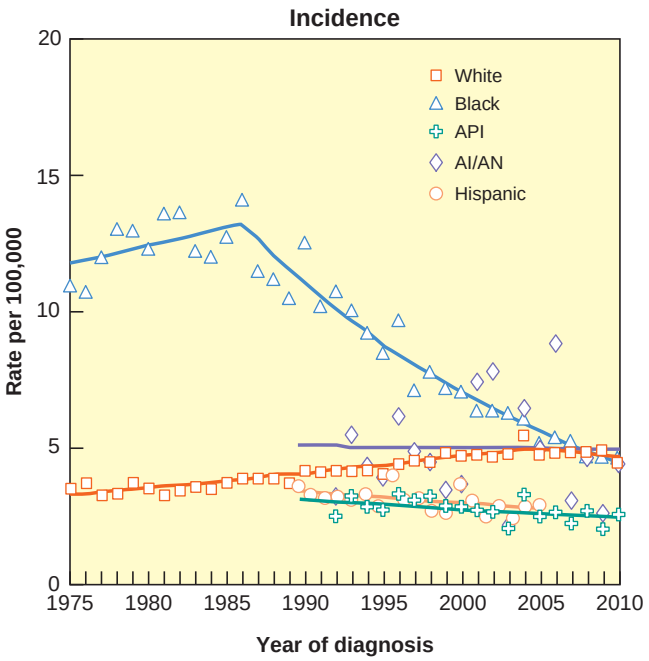

Figure 45.1 Surveillance, Epidemiology and End Results (SEER) age-adjusted esophageal cancer incidence rates in the United States. API, Asian/Pacific Islanders; AI/AN, American Indians/Alaska Natives.

tobacco use.[7] Cigarette smoking in adenocarcinoma of the esophagus leads to a twofold increase in risk for heavy smokers (more than one pack per day).[7,8] Quitting smoking does not appear to decrease the risk of adenocarcinoma, which remains elevated for decades after smoking cessation.[7,8] This suggests that tobacco carcinogens may affect carcinogenesis early on in esophageal adenocarcinoma, and, therefore, the decline in prevalence of smoking in the United States has not had an impact on the risk for the disease. Consistent with this hypothesis, cigarette smoking was recently identified as a risk factor for the development of Barrett's esophagus. Specifically, when analyzing data from five case-control studies involving 1,059 patients with Barrett's esophagus, 1,332 patients with gastroesophageal reflux disease (GERD), and 1,143 population-based controls, patients with Barrett's esophagus were significantly more likely to have ever smoked than either control cohort (odds ratio [OR] = 1.67 versus population-based controls; OR = 1.61 versus GERD controls). Furthermore, increasing the pack-years of smoking increased the risk of Barrett's esophagus.[9]

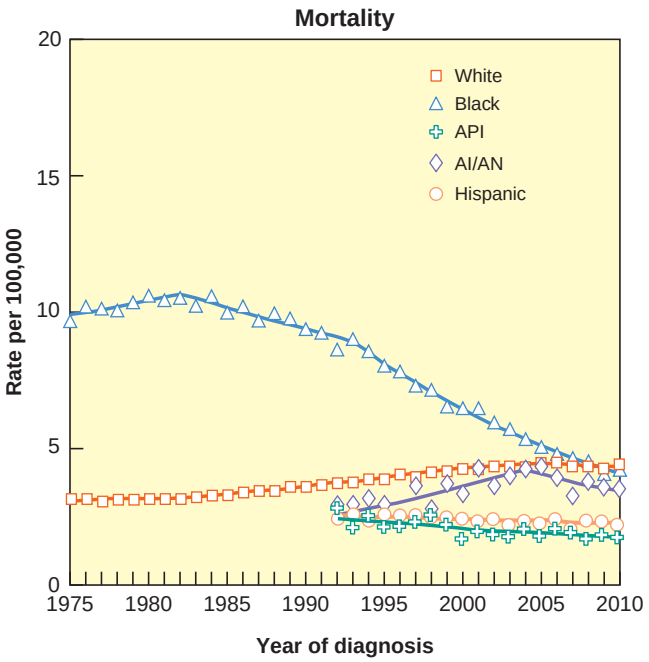

Figure 45.2 Surveillance, Epidemiology and End Results (SEER) age-adjusted esophageal cancer mortality rates in the United States. API, Asian/Pacific Islanders; AI/AN, American Indians/Alaska Natives.

Alcohol is a major contributing factor in the increased risk of esophageal squamous cell carcinoma in Western countries, likely accounting for 80% of squamous cell carcinoma of the esophagus in men in the United States.[6] A dose–response relationship exists between the amount of alcohol ingested and the risk of developing squamous cell carcinoma.[10,11] In most studies, the most commonly consumed beverage in a specific geographic region is the one most frequently associated with increased risk.[1] Although specific carcinogens may be present in a variety of alcoholic beverages, in all likelihood, it is alcohol itself—either as a mechanical irritant, promoter of dietary deficiency, or contributor to susceptibility to other carcinogens—that leads to carcinogenesis. Large population-based case-control studies in both the United States and Australia revealed no relationship between alcohol intake and risk of esophageal adenocarcinoma.[12]

Diet and Nutrition

For both squamous cell carcinoma and adenocarcinoma of the esophagus, case-control studies provide evidence of a protective effect of a diet enriched with fruits and vegetables, especially those eaten raw.[7,13] These food groups contain a number of micronutrients and dietary components such as vitamins A, C, and E; selenium; carotenoids; and fiber, which may prevent carcinogenesis. Deficiencies of the aforementioned nutrients and dietary components (in particular, selenium), have been associated with an increased risk of esophageal squamous cell carcinoma in some parts of the world.[14] Consumption of hot beverages has been suggested as a risk factor for esophageal cancer in South America.[15] More recently, a diet enriched with "animal products and related components" was significantly associated with the development of esophageal carcinoma (OR = 1.64; 95% confidence interval [CI], 1.06 to 2.55), whereas diets high in "vitamins and fiber" and "other polyunsaturated fatty acids and vitamin D" were protective of developing esophageal carcinoma (OR = 0.50 and 0.48, respectively).[16]

Socioeconomic Status

Low socioeconomic status as defined by income, education, or occupation is associated with an increased risk for esophageal squamous cell carcinoma and, to a lesser degree, for adenocarcinoma.[8,17] In the United States, it is estimated that 39% and 69% of squamous cell carcinomas of the esophagus in Caucasian men and African American men, respectively, are related to low annual income.[6] A number of occupational and industrial hazards, including exposure to perchloroethylene (e.g., dry cleaners, metal polishers), combustion products, and fossil fuels (e.g., chimney sweeps, printers, gas station attendants, asphalt and metal workers), silica and metal dust, and asbestos, as well as viral exposure via meat packing and slaughtering, have been suggested as possible risk factors for squamous cell carcinoma but not adenocarcinoma of the esophagus.[2]

Obesity

The prevalence of obesity in the United States markedly increased from 12.8% in the early 1960s to almost 23% between 1988 and 1994.[18] This upward trend parallels that seen for incidence rates of esophageal adenocarcinoma. Increased body mass index (BMI) is a risk factor for adenocarcinoma of the esophagus, and individuals

۰۲۱-۶۶۱۹۸۵۱۴ www.myuptodate.com دریافت آخرین نسخه آپتودیت آفلاین

with the highest BMI have up to a sevenfold greater risk of esophageal cancer than those with a low body mass index.[7,19–21] The mechanism by which obesity contributes to an increased risk of esophageal adenocarcinoma is uncertain, although the linkage between obesity and GERD is presumed to be a chief, but not the sole, factor. Recent reports suggest that the presence of abdominal/intra-abdominal or central obesity rather than BMI itself may increase the risk of Barrett's esophagus and, subsequently, esophageal adenocarcinoma.[22–24] Because of the influence of nutritional and socioeconomic factors, the risk of squamous cell carcinoma of the esophagus increases with decreasing BMI.

Gastroesophageal Reflux Disease

GERD has been implicated as one of the strongest risk factors for the development of adenocarcinoma of the esophagus.[25,26] Chronic reflux is associated with Barrett's esophagus, the premalignant precursor of esophageal adenocarcinoma. Population-based case-control studies that examined the relationship between symptomatic reflux and risk of adenocarcinoma of the esophagus have demonstrated that increased frequency, severity, and chronicity of reflux symptoms are associated with a 2- to 16-fold increased risk of adenocarcinoma of the esophagus, regardless of the presence of Barrett's esophagus.[25,26] Trends in incidence rates of GERD during the past 3 decades parallel the time trends of increasing incidence of adenocarcinoma in the United States.

Helicobacter pylori Infection

Infection with *Helicobacter pylori*, and particularly with cagA+ strains, is inversely associated with the risk of adenocarcinoma of the esophagus.[27,28] The mechanism of action is unclear, although an *H. pylori* infection can result in chronic atrophic gastritis, leading to decreased acid production and potentially reducing the development of Barrett's esophagus. Although infection by *H. pylori* cagA+ strains by itself may not increase the risk of squamous cell carcinoma, the concurrent presence of gastric atrophy and *H. pylori* infection has been reported to significantly increase the risk of squamous cell carcinoma.[29] Atrophic gastritis may promote bacterial overgrowth, leading to intragastric nitrosation, with the production of nitrosamines increasing the risk of esophageal squamous cell carcinoma.

Barrett's Esophagus

Barrett's esophagus is defined by the presence of intestinal metaplasia (mucin-producing goblet cells) in columnar cell–lined epithelium that replaces the normal squamous epithelium of the distal esophagus.[30–32] The appearance at endoscopy of salmon-colored columnar epithelium extending about the gastroesophageal junction contrasts with the pale, pink-colored normal squamous epithelium of the esophagus. Although other types of mucosa (gastric, fundic, or junctional type) have been identified in Barrett's esophagus, specialized intestinal metaplasia confirmed by histologic examination of biopsy specimens is required for the diagnosis of Barrett's esophagus. The absolute risk to develop adenocarcinoma in a year, once thought to be 1 in 100, is now estimated to be 0.12% to 0.33%.[33–36] Regardless of this revised absolute risk, Barrett's esophagus remains the single most important risk factor for developing esophageal adenocarcinoma, with a relative risk of 11.3 (95% CI, 8.8 to 14.4), implying that patients with Barrett's esophagus are 11-fold more likely to develop esophageal adenocarcinoma than individuals without Barrett's esophagus. Patients with short- and long-segment Barrett's esophagus are at risk of developing dysplasia and subsequently adenocarcinoma.[37]

The prevalence of Barrett's esophagus in the general population undergoing endoscopy is approximately 1.5%[38]; for those with reflux symptoms, the presence of Barrett's esophagus is 2.3%, and in those without reflux symptoms, it is 1.2%. The utility of screening patients with symptomatic reflux is unproven and unlikely to have a significant impact on reducing death from cancer because 40% of patients with adenocarcinoma of the esophagus have no history of reflux,[25] and fewer than 5% of patients undergoing resection for adenocarcinoma were documented to have Barrett's esophagus before seeking medical attention for their symptomatic cancer.[39] Despite this, the American Gastroenterological Association, the American College of Gastroenterology, and the American Society of Gastrointestinal Endoscopy[40–42] recommend selective screening of patients with GERD and multiple risk factors for esophageal cancer. Both medical and surgical antireflux therapies are effective at reducing or eliminating the symptoms of gastroesophageal reflux, but no clear-cut evidence exists that either therapy reduces the risk of esophageal adenocarcinoma. A randomized Veterans Affairs Cooperative Study of medical and surgical antireflux treatment in patients with severe GERD demonstrated superior control of reflux symptoms in the surgical treatment group but no difference between medical and surgical therapy groups in the incidence of esophageal cancer.[43] Overall survival was significantly decreased in the surgical treatment group as a result of an unexpected excess of deaths from heart disease.

All three U.S. medical societies mentioned previously recommend surveillance endoscopy for patients with the diagnosis of Barrett's esophagus, and the grade of dysplasia determines the endoscopy interval.[40–42] Uncontrolled studies suggest that adenocarcinomas identified by surveillance methods are detected at an earlier stage and are associated with a more favorable outcome after an esophagectomy.[44–46] However, the efficacy of surveillance endoscopy is unclear, and there are no convincing data demonstrating that surveillance prevents cancer or improves life expectancy.[47–49] Macdonald et al.[49] followed 143 patients with Barrett's esophagus for an average of 4.4 years with surveillance endoscopy and identified only one patient with asymptomatic esophageal adenocarcinoma. Similar findings were reported by O'Connor et al.[47] These studies suggest that routine surveillance of patients with Barrett's esophagus is unlikely to alter the natural history of this disease due to the low incidence of adenocarcinoma. Some authors suggest that surgical antireflux therapy causes regression of metaplastic epithelium or interrupts progression from Barrett's esophagus to low-grade and high-grade dysplasia,[50,51] but convincing evidence is lacking. A prospective, randomized trial of medical treatment versus open Nissen fundoplication in patients with Barrett's esophagus with or without low-grade dysplasia showed no statistically significant difference in progression to dysplasia or adenocarcinoma.[52] Observational studies suggest that the use of acid suppressive medial therapy—in particular, proton pump inhibitors—may decrease the risk of progression to either high-grade dysplasia or adenocarcinoma.[53] Progression from intestinal metaplasia to dysplasia in Barrett's esophagus signifies an unequivocal neoplastic change associated with the potential for malignant degeneration. Dysplasia is classified as low grade or high grade. The experience of the pathologist is crucial in correctly diagnosing high-grade dysplasia, which is the most important predictor for esophageal adenocarcinoma.[54] The differentiation of high-grade dysplasia from either low-grade dysplasia, indefinite dysplasia, or absence of dysplasia is straightforward (85% interobserver agreement). However, the diagnosis of low-grade dysplasia as differentiated from either indefinite dysplasia or findings negative for dysplasia is less reproducible (50% to 75% interobserver agreement).[55,56] Any degree of dysplasia warrants endoscopic surveillance. Annual endoscopy is recommended for those patients with low-grade dysplasia, and more frequent screening (i.e., every 3 months) is recommended for those patients with high-grade dysplasia if eradication therapy has not been instituted. The management of high-grade dysplasia is discussed in Treatment of Premalignant and T1 Disease, later in this chapter.

The proposed stepwise carcinogenic sequence in which specialized intestinal metaplasia proceeds to low-grade dysplasia, high-grade dysplasia, and frank carcinoma suggests a potential opportunity for chemoprevention to disrupt the succession to cancer. Buttar et al.,[57] recognizing that carcinogenesis in Barrett's esophagus is associated

۰۲۱-۶۶۱۹۸۵۱۴ www.myuptodate.com tahir99 - UnitedVRG دریافت آخرین نسخه آپتودیت آفلاین

with the increased expression of cyclooxygenase-2 (COX-2), examined the effect of COX-2 inhibitors on the development of Barrett's esophagus and adenocarcinoma in a preclinical model. Both selective and nonselective COX-2 inhibitors were effective at inhibiting Barrett's esophagus–related adenocarcinoma. A meta-analysis of two cohort and seven case-control studies comprising 1,813 cancer cases demonstrated a protective association between aspirin or nonsteroidal anti-inflammatory drugs (NSAID) and esophageal cancer.[58] These findings suggest that NSAIDs may act as potential chemopreventive agents. A small, phase IIb randomized placebo-controlled trial of celecoxib in 100 patients with Barrett's esophagus and low- or high-grade dysplasia failed to demonstrate a protective effect against progression of Barrett's dysplasia to adenocarcinoma.[59] The ongoing ASPECT trial in the United Kingdom, a phase III randomized study of aspirin and esomeprazole chemoprevention in Barrett's metaplasia, is evaluating the effect of high- and low-dose esomeprazole, with and without low-dose aspirin, on the progression of Barrett's esophagus to high-grade dysplasia or cancer. More than 2,500 patients have been enrolled in this chemoprevention trial with a planned follow-up of at least 8 years.

Tylosis

Tylosis (focal nonepidermolytic palmoplantar keratoderma) is a rare disease inherited in an autosomal-dominant manner that is characterized by hyperkeratosis of the palms and soles and esophageal papillomas. Patients with this condition exhibit abnormal maturation of squamous cells and inflammation within the esophagus and are at extremely high risk of developing esophageal cancer.[60,61] The tylosis esophageal cancer (*TOC*) gene has been mapped to 17q25 by linkage analysis of pedigrees.[62] The *TOC* gene is also frequently deleted in sporadic human esophageal cancers.[63,64] Envoplakin, which encodes a protein component of desmosomes that is expressed in esophageal keratinocytes, has been mapped to the *TOC* region[61]; however, no tylosis-specific mutations involving this gene have been observed.[65]

Plummer–Vinson/Paterson–Kelly Syndrome

Plummer–Vinson syndrome, also known as Paterson–Kelly syndrome, is characterized by iron-deficiency anemia, glossitis, cheilitis, brittle fingernails, splenomegaly, and esophageal webs. Approximately 10% of individuals with Plummer–Vinson/Paterson–Kelly syndrome develop hypopharyngeal or esophageal epidermoid carcinomas.[66] The mechanisms by which these tumors arise have not been fully defined, although nutritional deficiencies as well as chronic mucosal irritation from retained food particles at the level of the webs may contribute to the pathogenesis of these neoplasms.[67]

Caustic Injury

Squamous cell carcinomas may arise in lye strictures, often developing 40 to 50 years after a caustic injury.[68] The majority of these cancers are located in the middle third of the esophagus. The pathogenesis of these neoplasms may be similar to that implicated in esophageal cancers arising in patients with Plummer–Vinson/Paterson–Kelly syndrome. These cancers are often diagnosed late because chronic dysphagia and pain caused by the lye strictures obscure symptoms of esophageal cancer.

Achalasia

Achalasia is an idiopathic esophageal motility disorder characterized by increased basal pressure in the lower esophageal sphincter, incomplete relaxation of this sphincter after deglutition, and aperistalsis of the body of the esophagus. A 16- to 30-fold increase in esophageal squamous cancer risk has been noted in achalasia patients.[69,70] In a retrospective analysis, Aggestrup et al.[71] observed the development of esophageal carcinomas in 10 of 147 patients undergoing an esophagomyotomy for achalasia. These neoplasms are believed to result from prolonged irritation from retained food in the midesophagus and arise an average of 17 years after the onset of achalasia. The chronic dysphagia and pain attributable to megaesophagus contributes to their late diagnosis in achalasia patients.[72]

Human Papillomavirus Infection

Human papillomavirus (HPV) infection may contribute to the pathogenesis of esophageal squamous cell cancer in high-incidence areas in Asia and South Africa.[73] This oncogenic virus encodes two proteins (E6 and E7) that sequester the *Rb* and *p53* tumor suppressor gene products. Using polymerase chain reaction techniques, de Villiers et al.[74] detected HPV DNA sequences in 17% of esophageal squamous cell cancers in patients from China. In an additional study using similar techniques, Lavergne and de Villiers[75] identified a broad spectrum of HPV in approximately one-third of esophageal cancer specimens obtained from patients living in high-incidence areas in China and South Africa. Shibagaki et al.[76] detected HPV sequences in 15 of 72 (21%) esophageal cancer specimens obtained from Japanese patients. In contrast, neither evidence of HPV infection nor HPV DNA sequences have been observed in cancers arising in low-incidence areas.[77–80]

Prior Aerodigestive Tract Malignancy

Patients with upper aerodigestive tract cancers develop second primary cancers at a rate of approximately 4% per year.[81] Nearly 10% of secondary neoplasms arising in patients with prior histories of oropharyngeal of lung carcinoma arise in the esophagus.[82–84] Interestingly, *p53* mutational analysis of multiple primary cancers of the aerodigestive tract in 17 patients demonstrated complete discordance of the *p53* genotype between separate primary tumors from the same patient, which suggests that *p53* is not functioning as a tumor susceptibility gene in this setting.[85]

Comparative Genomics

Cancers of the esophagus and stomach are heterogenous and are noted to have genomic instability, as measured by greater somatic copy number alterations when compared with lower gastrointestinal tract tumors.[86] For esophageal and gastroesophageal junction (GEJ) adenocarcinomas, amplification of certain genes rather than gene mutations may be more important drivers of oncogenesis, including targetable kinases such as epidermal growth factor receptor (EGFR), ERBB2, fibroblast growth factor receptor (FGFR)1 and 2, and MET. The most commonly affected genes by mutation include TP53 and CDKN2A.[87] A recent study reported the results of whole-exome sequencing of esophageal adenocarcinoma and esophageal squamous cell carcinoma, and identified notable differences that support the different epidemiology and risk factors for these two distinct diseases.[88] In addition to mutations in TP53, investigators identified NOTCH1 as an important gene in esophageal squamous cell carcinoma development. Also of note, the investigators found conserved mutations in matched samples of Barrett's esophagus and esophageal adenocarcinoma, supporting the progressive molecular pathogenesis of esophageal adenocarcinoma.[88]

APPLIED ANATOMY AND HISTOLOGY

Anatomy

The esophagus bridges three anatomic compartments: the neck, the thorax, and the abdomen (Fig. 45.3). The esophagus extends from the cricopharyngeus muscle at the level of the cricoid

۰۲۱-۶۶۱۹۸۵۱۴ www.myuptodate.com دریافت آخرین نسخه آپتودیت آفلاین

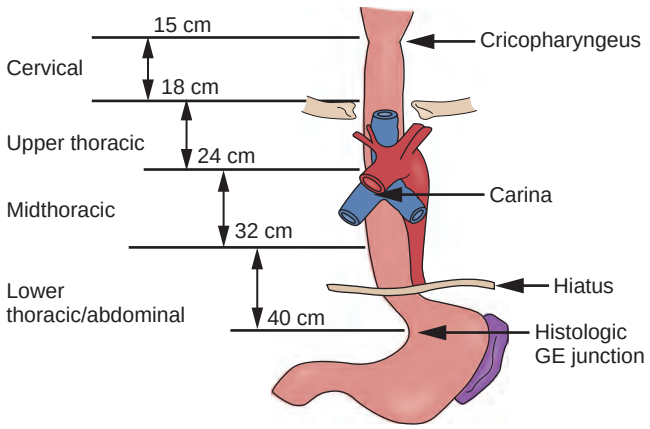

Figure 45.3 Anatomy of the esophagus with landmarks and recorded distance from the incisors used to divide the esophagus into topographic compartments. GE, gastroesophageal.

cartilage to the gastroesophageal junction.[89] The borders of the cervical esophagus span from the cricopharyngeus to the thoracic inlet (approximately 18 cm from the incisors). The remainder of the esophagus is commonly divided into thirds, with the upper third extending from the thoracic inlet to the carina (approximately 24 cm from the incisors), the middle third extending from the carina to the inferior pulmonary veins (32 cm from the incisors), and the distal esophagus traversing the remaining distance into the abdomen to the GEJ (40 cm from the incisors). Squamous cell carcinoma of the esophagus is the predominant histology in the cervical esophagus and upper and middle thirds (above the pulmonary vein) of the thoracic esophagus, whereas adenocarcinoma predominates in the distal esophagus.

Adenocarcinomas of the GEJ present a unique challenge because appropriate management of these tumors as either esophageal or gastric cancers has been uncertain. Siewert et al.[81] have offered a classification system based on demographics, histopathologic variables, and patterns of lymphatic spread that provides clarity, is well established, and has been generally accepted worldwide (Fig. 45.4). In this classification scheme, type I tumors are considered adenocarcinomas of the distal esophagus and type II and III lesions are classified as gastric cancers (cardia and subcardia). This classification system allows for a tailored and consistent surgical approach to these tumors as well as consistency in reporting outcome results associated with therapeutic interventions. However, it should be noted that in the most recent guidelines established by the American Joint Committee on Cancer, GEJ tumors are included under the esophageal cancer staging classification.[90]

The pattern of lymphatic drainage of the esophagus influences the choice of surgical approach, based on tumor location in the esophagus (Fig. 45.5). Tumors of the cervical and upper third of the thoracic esophagus drain to cervical and superior mediastinal lymph nodes. Tumors of the middle third of the esophagus drain both cephalad and caudad with lymph nodes at risk in the paratracheal, hilar, subcarinal, periesophageal, and pericardial nodal basins. Lesions in the distal esophagus primarily drain to lymph nodes in the lower mediastinum and celiac axis region. Because of the extensive lymphatic network within the wall of the esophagus, skip metastases for upper third lesions have been noted in celiac axis nodal basins, and likewise, cervical lymph node metastases have been noted in as many as 30% of patients with distal esophageal lesions. Some surgeons recommend a more radical oncologic procedure, a combined transthoracic and abdominal approach for lesions of the middle and distal esophagus,[91,92] and others recommend a three-field (cervical, mediastinal, and abdominal) lymphadenectomy for all tumors of the middle through distal esophagus.[93,94] However, lymph node metastases are initially limited in an overwhelming majority of patients to regional lymph nodes. Lymph node involvement in lymphatic basins distant from the primary tumor are rarely identified unless metastases to regional lymph nodes have already occurred,[95] which suggests the potential of sentinel lymph node sampling to direct surgical dissection.[96]

Histology

Squamous cell carcinomas account for approximately 40% of esophageal malignancies diagnosed in the United States and the majority of cases arising in high-incidence areas throughout the world.[97] Approximately 60% of these neoplasms are located in the middle third of the esophagus, whereas 30% and 10% arise in the distal third and proximal third of the intrathoracic esophagus, respectively. These tumors are associated with contiguous or noncontiguous carcinoma in situ as well as widespread submucosal lymphatic dissemination.

Adenocarcinomas frequently arise in the context of Barrett's esophagus; because of this, these tumors occur in the distal third of the esophagus. No significant survival differences have been noted in adenocarcinoma patients compared with individuals with squamous cell cancers.

Rarer cancers of the esophagus include squamous cell carcinoma with sarcomatous features, adenoid cystic, and mucoepidermoid carcinomas. These neoplasms are indistinguishable clinically and prognostically from the more common types of esophageal carcinoma.

Small cell carcinomas account for approximately 1% of esophageal malignancies and arise from argyrophilic cells in the basal

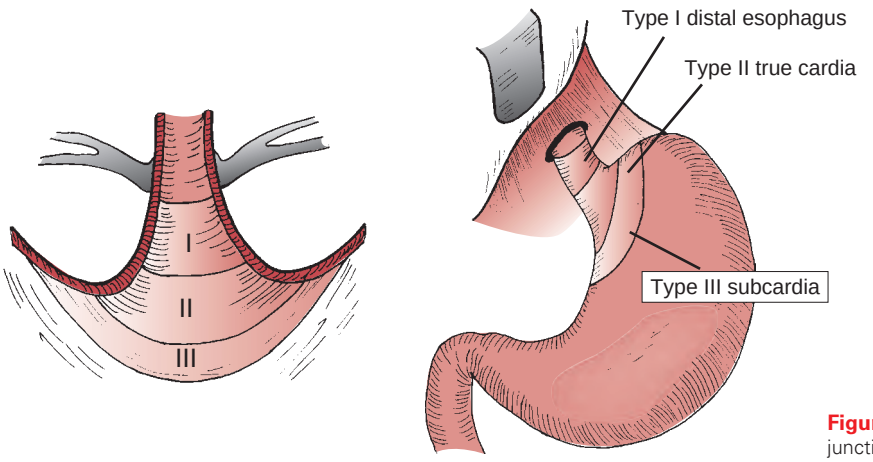

Figure 45.4 Anatomic classification of gastroesophageal junction tumors.

۰۲۱-۶۶۱۹۸۵۱۴ www.myuptodate.com tahir99 - UnitedVRG دریافت آخرین نسخه آپتودیت آفلاین

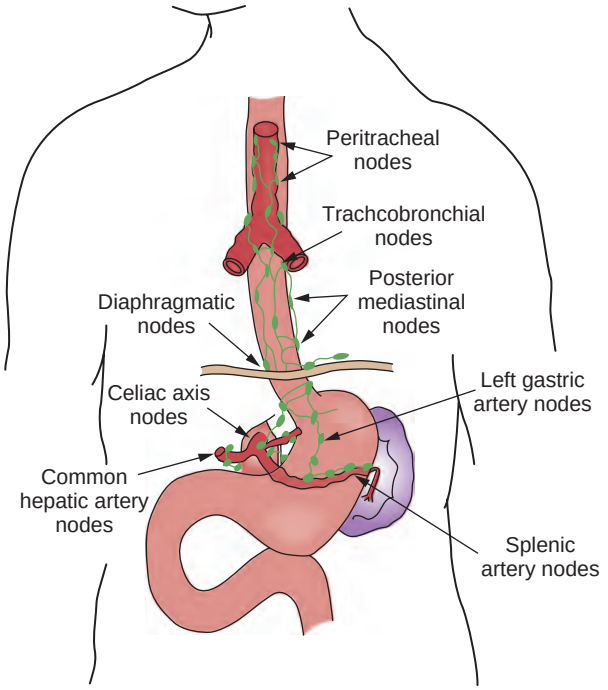

Figure 45.5 Lymphatic drainage of the esophagus with anatomically defined lymph node basins.

layer of the squamous epithelium. These neoplasms are usually located in the middle or lower third of the esophagus and may be associated with an ectopic production of a variety of hormones, including parathormone, secretin, granulocyte colony-stimulation factor, and gastrin-releasing peptide; individuals with these cancers often present with systemic disease.[98–100] Recent series have reported patients with locally advanced disease treated with systemic chemotherapy in combination with either radiation therapy, surgery, or both, with some patients achieving long-term disease-free survival.[101]

Leiomyosarcoma is the most common mesenchymal tumor that affects the esophagus, still accounting for less than 1% of esophageal malignancies. These neoplasms are lower third tumors presenting as bulky masses with hemorrhaging and necrosis. Malignant lymphoma and Hodgkin lymphoma rarely involve the esophagus and is usually secondary to extension from other sites. Patients with AIDS may exhibit Kaposi sarcoma involving the esophagus. Malignant melanoma involving the esophagus is exceedingly rare and presents as a bulky polypoid intraesophageal tumor of varying color depending on melanin production.

NATURAL HISTORY AND PATTERNS OF FAILURE

At presentation, the overwhelming majority of patients have locally or regionally advanced or disseminated cancer, irrespective of histologic type.[4,102] The lack of a serosal envelope and the rich submucosal lymphatic network of the esophagus lead to extensive local infiltration and lymph node involvement. Evidence suggests that occult micrometastases are invariably present, and recurrence patterns confirm that distant failure is a significant and universally fatal component of relapse.[103–107] Bone marrow samples obtained during rib resections performed at an esophagectomy revealed disseminated tumor cells in up to 90% of patients sampled.[108,109] The lung, liver, and bone are the most common sites of distant disease, with depth of tumor invasion and lymph node involvement predictive of tumor dissemination.[89,103,104]

Median survival after esophagectomy for patients with localized disease is 15 to 18 months with a 5-year overall survival rate of 20% to 25%. Patterns of failure after an esophagectomy suggest that both the location of tumor and histologic type may influence the distribution of recurrence. In patients with cancers of the upper and middle thirds of the esophagus, which are predominately squamous cell carcinomas, local–regional recurrence predominates over distant recurrence, whereas in patients with lesions of the lower third, where adenocarcinomas are more frequently located, distant recurrence is more common.[103,104] Only a very small percentage of patients (fewer than 5%) develop a clinically evident recurrence at cervical sites.[95]

The addition of chemotherapy, radiotherapy, or chemoradiation to surgery alters patterns of failure, although reported results are not consistent. Preoperative radiotherapy and preoperative chemoradiation may reduce the rate of local–regional recurrence but have no obvious effect on the rate of distant metastases.[107–111] In two prospective randomized trials recently updated with a long-term follow-up of preoperative chemotherapy plus surgery versus surgery alone that reported patterns of failure, one study showed a slight but not statistically significant decrease in distant relapse with chemotherapy,[105,112] whereas the other demonstrated equivalent distant recurrence rates in both the preoperative chemotherapy and surgery-alone arms.[106,113] Treatment failure patterns after definitive chemoradiation without surgical resection reveal that the concurrent administration of chemotherapy and radiotherapy provides better local control than radiotherapy alone, and that the administration of chemotherapy may reduce systemic recurrence; however, the long-term follow-up of both randomized and nonrandomized patients treated with primary chemoradiation failed to indicate a clear reduction in distant disease recurrence compared with radiation therapy alone.[114] Although the addition of surgery further reduces local failure from 45% to 32%,[115] it does not diminish the systemic recurrence and, in fact, may enhance it by allowing patients to manifest distant disease because they do not succumb to local–regional failure.[116,117] These patterns of relapse suggest that any further improvement in overall outcome for patients with esophageal cancer will be achieved through advances in systemic therapy.

CLINICAL PRESENTATION

The most noticeable symptoms are dysphagia and weight loss. Dysphagia signifies locally advanced disease or distant metastases, or both. Patients describe progressive dysphagia, with initial difficulty in swallowing solids, then liquids. Control of this single symptom impacts most on the patient's quality of life. Patients with squamous cell carcinoma of the esophagus more often have a history of tobacco or alcohol abuse, or both. Weight loss is seen in approximately 90% of patients with squamous cell carcinoma. Patients with adenocarcinoma of the esophagus tend to be Caucasian males from middle to upper socioeconomic classes who are overweight, have a symptomatic gastroesophageal reflux, and have been treated with antireflux therapy.

Approximately 20% of patients experience odynophagia (painful swallowing). Additional presenting symptoms include dull retrosternal pain, bone pain secondary to bone metastases, and cough or hoarseness secondary to paratracheal nodal or recurrent laryngeal nerve involvement. These types of symptoms suggest unresectable locally advanced disease or metastases. Unusual presentations are pneumonia secondary to tracheoesophageal fistula or exsanguinating hemorrhage due to aortic invasion.

DIAGNOSTIC STUDIES AND PRETREATMENT STAGING

Patients with symptoms of dysphagia should undergo an upper endoscopy and a biopsy to establish a tissue diagnosis. Biopsies or cytologic brushings have a diagnostic accuracy approaching 100%.[118,119]

۰۲۱-۶۶۱۹۸۵۱۴ www.myuptodate.com دریافت آخرین نسخه آپتودیت آفلاین

A targeted biopsy can be enhanced by the use of chromoendoscopy techniques using vital dyes, including indigo carmine, Lugol iodine solution, methylene blue, and toluidine blue.[120,121] Autofluorescence imaging and narrow band imaging are emerging endoscopic techniques that allow for a detailed inspection of mucosa.[122–125]

A focused history taking should elicit information on predisposing factors for esophageal cancer, including tobacco use, alcohol use, symptomatic reflux, a diagnosis of Barrett's esophagus, and history of head and neck or thoracic malignancy. Prior surgery on the stomach or colon may influence the choice of reconstructive conduit to restore alimentary continuity at the time of an esophagectomy. Findings on history and physical examination that would prompt further diagnostic testing include hoarseness, cervical or supraclavicular lymphadenopathy, pleural effusion, or new onset of bone pain.

A chest radiography and a liquid oral contrast examination of the esophagus and stomach have been replaced by a computed tomography (CT) scan and a flexible endoscopy. An esophagogastroscopy allows for a precise evaluation of the extent of esophageal and gastric involvement and can precisely measure the distance of the tumor from the incisors to appropriately categorize the tumor's location. An upper endoscopy also allows for the identification of "skip" lesions or second primaries as well as indicates the presence and extent of Barrett's esophagus. A bronchoscopy should be reserved for those patients with tumors of the middle and upper esophagus to rule out invasion of the membranous trachea and possible tracheoesophageal fistula, although an endoscopic ultrasound is now the procedure of choice to identify these unusual manifestations.

Pretreatment staging procedures establish the depth of esophageal wall penetration, regional lymph nodes, and the presence of distant metastases so that patients can be guided to appropriate treatment. A CT scan of the chest and abdomen is mandatory. A recent single institution review of 201 CT scans in 99 patients undergoing staging for esophageal cancer indicated that imaging of the pelvis did not contribute added staging information, and it may not need to be routinely performed.[126] CT scans are highly accurate (approaching 100%) at detecting liver or lung metastases and suggesting peritoneal carcinomatosis (e.g., ascites, omental infiltration, peritoneal tumor studding).[127–129] Accuracy for detecting aortic involvement or tracheobronchial invasion exceeds 90%.[128,130,131] A CT scan is inaccurate in determining T stage and N stage.[127,128,130,132–134] The accuracy of endoscopic ultrasonography (EUS) in determining both T and N stage is a function of its ability to clearly delineate the multiple layers of the esophageal wall[135,136] and its use of multiple criteria, including shape, border pattern, echogenicity, and size, to determine lymph node involvement.[137,138] EUS is superior to CT scans in both T and N staging of esophageal cancer.[139,140] The overall accuracy for T staging is approximately 85%, and for N staging it is approximately 75%.[141] The accuracy of determining lymph node involvement has been increased to 85% to 100% with the use of linear-array EUS with a channel that allows for passage of a needle to perform tissue aspiration for cytology.[134,142,143] EUS is highly operator dependent and is limited in its ability to define relatively superficial lesions as either T1 or T2.[141,144,145] This distinction is critical to allow for the use of minimal resection techniques for T1 lesions and to avoid preoperative chemoradiation for T1 and T2 tumors. Miniprobe high-frequency (20 MHz) sonographic catheters that can be passed through the working channel of the standard endoscope are now being used and provide improved accuracy.[146,148] A new generation of endoscopes that are thin caliber may traverse almost all obstructing lesions, allowing for an EUS assessment.[148] The accuracy of EUS in assessing a response to induction chemoradiation is severely limited, and its use frequently leads to overstaging because the fibrotic changes induced by treatment mimic residual tumor,[149,150] although recent data may indicate some utility for posttherapy EUS.[151]

The fluorine-18 (^{18}F) fluorodeoxyglucose (FDG) positron emission tomography (PET) scan is being widely applied in the management of esophageal cancer. The accuracy of FDG-PET scans in assessing regional lymph nodes falls somewhere between the low and high accuracy of CT scans and EUS, respectively.[152,153] In the detection of distant metastases, an FDG-PET scan is superior to CT, with a sensitivity, specificity, and accuracy all in the range of 80% to 90%.[153,154] PET scans, in combination with CT (PET-CT fusion or hybrid FDG-PET/CT) scans, further improves specificity and accuracy of noninvasive staging.[155] This leads to the detection of unsuspected metastatic disease (upstaging) in 15% of patients, which leads to alteration of the intended treatment plan in at least 20% of patients. Currently, the utility of PET to detect distant disease not identified by other imaging modalities confirms a role for PET that is complementary to other staging procedures, although it should not supplant them.

FDG-PET may also have value in evaluating response to chemotherapy and radiotherapy. Weber et al.[156] demonstrated that decreased FDG uptake significantly correlated with pathologically confirmed response in patients treated with induction chemotherapy before esophagectomy for esophageal adenocarcinoma. A prospective validation study confirmed that a decrease in the standard uptake value of 35% or more during preoperative chemotherapy may predict histologic response and is associated with improved survival and decreased recurrence.[157] Brucher et al.,[158] from the same institution, Technische Universitat Munchen, showed a similar result of decreased FDG uptake in responders compared with nonresponders in patients with squamous cell carcinoma of the esophagus treated with preoperative chemoradiation. The MUNICON trial from the group led by Lordick et al.[159] examined PET scan response during induction chemotherapy in 110 patients with adenocarcinoma of the GEJ. PET scan nonresponders (54 patients) assessed after 2 weeks of induction chemotherapy were referred for immediate surgery rather than continuing with the full 3-month course of preoperative chemotherapy. Survival in these patients (median, 26 months) was comparable to nonresponding patients in a preceding trial (median, 18 months) who continued the full 3 months of chemotherapy prior to surgery, indicating that discontinuation of an ineffective therapy and referral for earlier surgery did not compromise outcome. Survival, however, was inferior in the PET-nonresponding patients compared with the PET responders. Although PET response may identify patients in whom ineffective preoperative therapy should be discontinued, whether or not referral of such patients for alternative chemotherapy, or chemoradiation, is warranted remains to be established. The MUNICON II trial explored whether PET scan nonresponders could have their outcome improved by further treatment with salvage neoadjuvant chemoradiotherapy consisting of single-agent cisplatin combined with 3,000 cGy of radiation therapy followed by surgery. When comparing PET scan nonresponders from MUNICON II treated with additional chemoradiation to nonresponders from the MUNICON trial, the R0 resection rate was not improved and there was no difference in either time to progression or overall survival across trials.[160] The small sample size and the utilization of suboptimal chemotherapy and radiotherapy dosing on the PET scan nonresponder arm make this trial difficult to interpret. One series of patients treated with induction chemotherapy, followed with serial PET scans, identified some patients who progressed on induction chemotherapy. Several of these patients achieved durable disease control, including pathologic complete response, when changed to an alternative chemotherapy during radiation therapy, suggesting that salvage with alternative treatment may be possible.[161] Although pathologic responses on this trial were seen in virtually only early PET scan responding patients, other trials have not shown a clear correlation with early response seen on PET scan during induction chemotherapy with subsequent pathologic response to chemoradiotherapy.[161] Two recent systematic reviews of the current available literature that addressed the evaluation of tumor response by PET scan to neoadjuvant therapy concluded that, although PET scans are the best imaging modality available to assess response, the current data

۰۲۱-۶۶۱۹۸۵۱۴ www.myuptodate.com tahir99 - UnitedVRG دریافت آخرین نسخه آپتودیت آفلاین

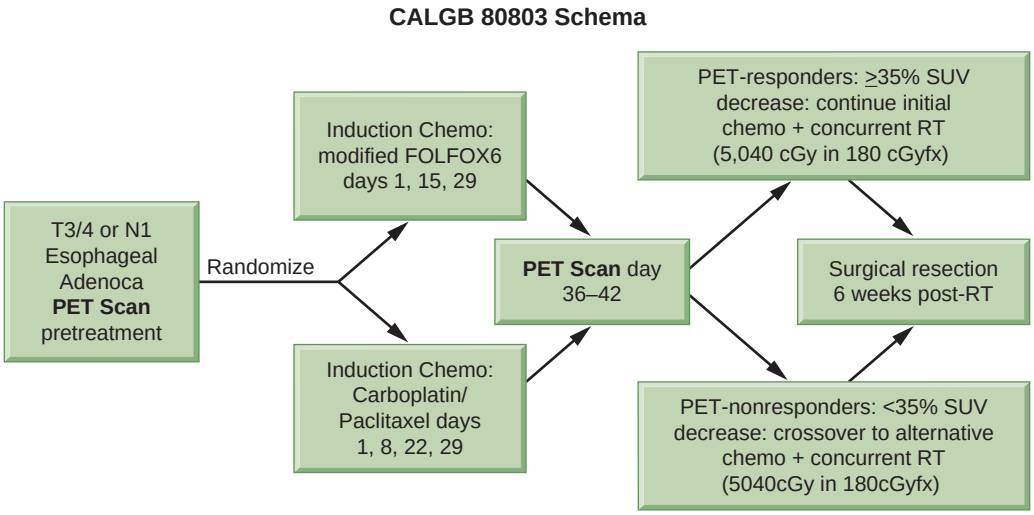
CALGB 80803 Schema
T3/4 or N1 Esophageal Adenoca PET Scan pretreatment
Randomize
Induction Chemo: modified FOLFOX6 days 1, 15, 29
Induction Chemo: Carboplatin/ Paclitaxel days 1, 8, 22, 29
PET Scan day 36–42
PET-responders: ≥35% SUV decrease: continue initial chemo + concurrent RT (5,040 cGy in 180 cGyfx)
Surgical resection 6 weeks post-RT
PET-nonresponders: <35% SUV decrease: crossover to alternative chemo + concurrent RT (5040cGy in 180cGyfx)

Figure 45.6 Alliance Intergroup randomized phase II trial (CALGB 80803) in resectable adenocarcinoma of the esophagus. SUV, standard update value; RT, radiation therapy.

do not support recommending the routine use of PET scans to guide therapeutic decisions.[162,163] The ALLIANCE Cooperative Group is currently prospectively evaluating the use of PET scans to direct preoperative chemoradiotherapy. Accrual is ongoing to a randomized phase II trial (CALGB 80803) designed to answer the question of whether nonresponders to induction preoperative chemotherapy subsequently treated with a nonoverlapping chemoradiotherapy regimen prior to surgery improves outcome (Fig 45.6).

Minimally invasive surgical techniques (laparoscopy, thoracoscopy, or both) are being used for the staging of both local–regional and distant disease. Performing laparoscopy as the initial procedure at the time of a planned esophagectomy adds little in the way of time and cost to the procedure and allows for the detection of unsuspected distant metastases, which spares the morbidity of laparotomy in 10% to 15% of cases.[164,165] Although studies suggest improved pretreatment staging with minimally invasive surgical approaches,[166–168] such approaches have not been embraced because of the morbidity, length of hospital stay, and cost associated with what is considered an additional procedure.

A study comparing the health-care costs and efficacy of staging procedures, including CT scans, EUS fine-needle aspirations (FNA), PET scans, and thoracoscopies or laparoscopies reported that CT scans plus EUS FNAs were the least expensive and offered the most quality-adjusted life-years on average than all the other strategies. PET scans plus EUS FNAs were somewhat more effective but also more expensive.[169]

PATHOLOGIC STAGING

The most recent guidelines established by the American Joint Committee on Cancer (AJCC) for the staging of esophageal cancer are outlined in Tables 45.1 and 45.2.[90] Changes between the current (seventh edition) and immediate past staging guidelines are highlighted. The tumor location is now defined by the position of the proximal edge of the tumor and is designated as upper, middle, or lower esophagus. Esophagogastric junction tumors are now included in the esophageal cancer staging schema. The primary tumor (T) stage is based on depth of tumor invasion into and through the wall of the esophagus. T stage is now listed as high-grade dysplasia that includes all noninvasive neoplastic epithelium, which was formerly called carcinoma in situ. T1 tumors are now subclassified as T1a (the tumor invades the lamina propria or muscularis mucosae) and T1b (the tumor invades the submucosa). T4 tumors that invade adjacent structures are now subclassified as

TABLE 45.1

Tumor (T), Node (N), Metastasis (M) Staging System for Esophageal Cancer

Primary Tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	High grade dysplasia[a]
T1	Tumor invades lumina propria, muscularis mucosae, or submucosa
T1a	Tumor invades lamina propria or muscularis mucosae
T1b	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades adventitia
T4	Tumor invades adjacent structures
T4a	Resectable tumor invading pleura, pericardium, or diaphragm
T4b	Unresectable tumor invading other adjacent structures, such as aorta, vertebral body, trachea, etc.
Regional Lymph Nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis involving 1 to 2 nodes
N2	Regional lymph node metastases involving 3 to 6 nodes
N3	Regional lymph node metastases involving 7 or more nodes
Distant Metastasis (M)	
M0	No distant metastasis (no pathologic M0; use clinic M to complete stage group)
M1	Distant metastasis

[a] High-grade dysplasia includes all noninvasive neoplastic epithelium that was formerly called carcinoma in situ, a diagnosis that is no longer used for columnar mucosae anywhere in the gastrointestinal tract.

Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the *AJCC Cancer Staging Manual*, Seventh Edition (2010) published by Springer Science and Business Media LLC, www.springer.com, page 109.

۰۲۱-۶۶۱۹۸۵۱۴ www.myuptodate.com دریافت آخرین نسخه آپتودیت آفلاین

TABLE 45.2

Classification of Staging Groupings for Esophageal Cancer

Squamous Cell Carcinoma[a]					
Group	**T**	**N**	**M**	**Grade**	**Tumor Location[b]**
0	Tis (HGD)	N0	M0	1	Any
IA	T1	N0	M0	1, X	Any
IB	T1	N0	M0	2–3	Any
	T2–3	N0	M0	1, X	Lower, X
IIA	T2–3	N0	M0	1, X	Upper, middle
	T2–3	N0	M0	2–3	Lower, X
IIB	T2–3	N0	M0	2–3	Upper, middle
	T1–2	N1	M0	Any	Any
IIIA	T1–2	N2	M0	Any	Any
	T3	N1	M0	Any	Any
	T4a	N0	M0	Any	Any
IIIB	T3	N2	M0	Any	Any
IIIC	T4a	N1–2	M0	Any	Any
	T4b	Any	M0	Any	Any
	Any	N3	M0	Any	Any
IV	Any	Any	M1	Any	Any
Adenocarcinoma					
Group	**T**	**N**	**M**	**Grade**	
0	Tis (HGD)	N0	M0	1, X	
IA	T1	N0	M0	1–2, X	
IB	T1	N0	M0	3	
	T2	N0	M0	1–2, X	
IIA	T2	N0	M0	3	
IIB	T3	N0	M0	Any	
	T1–2	N1	M0	Any	
IIIA	T1–2	N2	M0	Any	
	T3	N1	M0	Any	
	T4a	N0	M0	Any	
IIIB	T3	N2	M0	Any	
IIIC	T4a	N1–2	M0	Any	
	T4b	Any	M0	Any	
	Any	N3	M0	Any	
IV	Any	Any	M1	Any	
Stage unknown					

[a] Or mixed histology including a squamous component, or not otherwise specified.
[b] Location of the primary cancer site is defined by the position of the upper (proximal) edge of the tumor in the esophagus.
Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the *AJCC Cancer Staging Manual*, Seventh Edition (2010) published by Springer Science and Business Media LLC, www.springer.com, page 109.

T4a (a resectable tumor invading the pleura, pericardium, or diaphragm) and T4b (an unresectable tumor). The nodal (N) stage is determined by the presence of involved regional lymph nodes and is now subclassified according to the number of regional lymph nodes involved. The subclassification of metastasis (M) based on distant lymph node involvement (e.g., celiac node metastases for distal esophageal tumors) is no longer used. An analysis of 336 esophageal cancer patients who underwent resection alone recommended that the AJCC system be revised to take into account the number of involved lymph nodes, and that 18 lymph nodes should be the minimum harvested to provide for an accurate staging.[170] The current AJCC guidelines do not specify the number of lymph nodes to be removed, but instead suggest that the surgeon resect as many lymph nodes as possible while minimizing morbidity. Future refinements in the staging of esophageal cancer may result from incorporation of computational modalities such as nomograms and artificial neural networks that may predict outcome better than the TNM-based staging systems.[171] Successive pathologically determined stage groups are predictive of length of survival.[89,102] Overall survival for adenocarcinoma and squamous cell carcinoma in patients treated with surgery alone, as staged by the new AJCC staging system is outlined in Figure 45.7.[172]

TREATMENT

The paucity of appropriately designed studies to scientifically determine the most effective therapeutic strategy in esophageal cancer fuels an ongoing debate and undermines the potential for achieving consensus. Although there is no disagreement that esophageal resection prevents progression from high-grade dysplasia to invasive carcinoma and is curative for T1 lesions limited to the mucosa, the morbidity and mortality associated with esophagectomy has created appropriate enthusiasm for alternative approaches such as mucosal ablation and endoscopic resection. Surgery has always been considered the most effective way of ensuring both local–regional control and long-term survival for patients with tumors invading into or beyond the submucosa with or without lymph node involvement. Some investigators suggest that extending the limits of resection will further improve an outcome. However, surgery alone or any other single modality fails in most patients, which has led oncologists to embrace chemoradiation and some to question the necessity for surgical intervention. Chemoradiation with or without resection is the most common therapeutic regimen offered to patients with locally advanced (stage II or III) esophageal carcinoma in the United States and its use has increased dramatically in the past decade.[102,173]

Treatment of Premalignant and T1 Disease (Localized to the Mucosa Only)

High-grade dysplasia in Barrett's esophagus is the most powerful predictor of subsequent invasive adenocarcinoma and is associated with a per-year cancer incidence of 6%, thereby warranting therapeutic intervention. The rationale for esophagectomy is that resection completely eradicates the mucosa at risk, which prevents progression to invasive carcinoma. This is supported by older surgical series reporting previously unidentified invasive cancer, which was present in up to 40% of resected specimens.[174–177] The argument against esophagectomies is that most patients with high-grade dysplasia do not develop invasive carcinoma in their lifetimes and, in the era of endoscopic resection, that early cancers can be effectively addressed without an esophagectomy. Those supporting endoscopic methods, ranging from surveillance to mucosal ablative and resection techniques, argue that this allows for the identification of patients with an early invasive lesion that is readily amenable to cure or elimination of the mucosa at risk, thus preventing progression. Indeed, patients with superficial invasive tumors confined to the mucosa, and those with T1a disease in particular, have little or no risk of lymph node metastases[178,179] and are considered candidates for endoscopic therapies.

Surveillance

Endoscopic surveillance is based on the assumptions that the majority of patients will not progress to invasive carcinoma[180] and

۰۲۱-۶۶۱۹۸۵۱۴ www.myuptodate.com tahir99 - UnitedVRG دریافت آخرین نسخه آپتودیت آفلاین

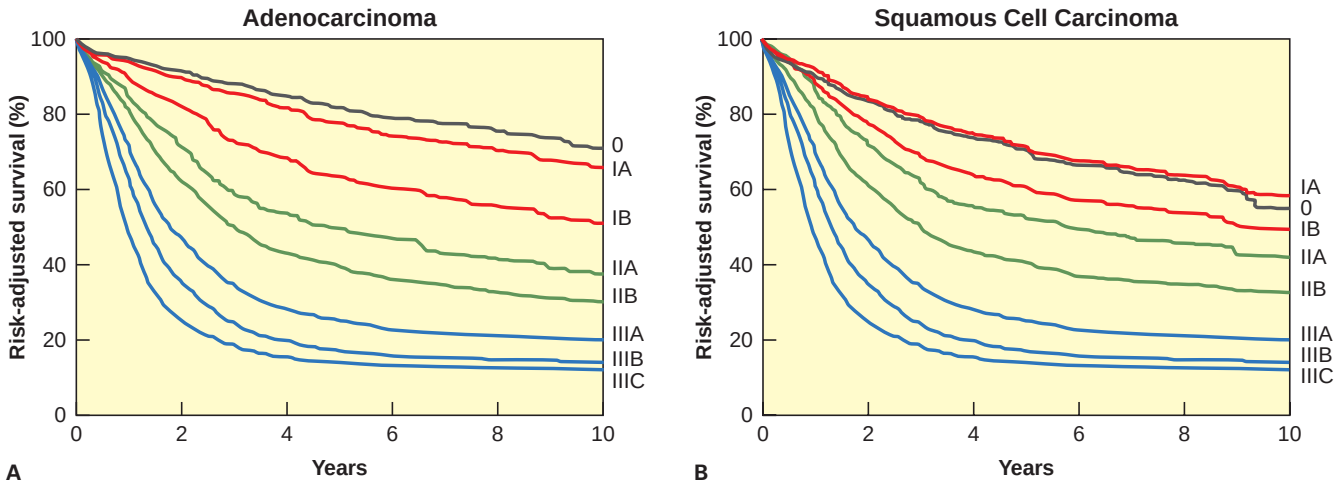

Figure 45.7 Risk-adjusted survival for **(A)** adenocarcinoma and **(B)** squamous cell carcinoma of the esophagus according to stage groups based on the seventh edition of the American Joint Commission on Cancer staging system.

that actual cancers detected by surveillance are at an earlier stage and are therefore curable.[181] Studies demonstrating that patients with Barrett's esophagus–associated adenocarcinomas detected by surveillance have an earlier stage of disease and have better survival than those detected at an initial endoscopy provide supportive evidence for surveillance.[44–46,174] Critics counter this argument with reports identifying invasive adenocarcinoma in up to 45% of esophagectomy specimens from patients with a diagnosis of high-grade dysplasia.[175–177] Proponents of surveillance management argue that these patients were not on an endoscopic surveillance program with strict biopsy criteria, and that strict pathologic criteria of invasive disease (submucosal invasion or beyond) were not utilized.[182]

Proposed guidelines for surveillance include serial endoscopy at 3- to 6-month intervals with multiple four-quadrant biopsies at 1- to 2-cm intervals.[33] The downside of endoscopic vigilance is that in a certain percentage of patients, invasive cancer goes undetected and the patients will not be candidates for potentially curative treatment.[183–185] This must be weighed against the morbidity and mortality of an esophagectomy. It is important to note that the extent of high-grade dysplasia does not predict the presence of occult adenocarcinoma identified at an esophagectomy and, therefore, cannot necessarily be applied to a subjective quantification of disease.[186]

Ablative Methods

The mechanism of action of all mucosal ablative techniques, including photodynamic therapy (PDT), laser ablation, multipolar electrocoagulation, argon plasma coagulation, and radiofrequency ablation, is destruction of the mucosal layer. The premise for managing high-grade dysplasia with endoscopic ablative therapy is that mucosal injury in an acid-controlled environment via proton-pump inhibitors eliminates the premalignant mucosa and resurfaces the esophageal lining with regenerated squamous epithelium.[181]

PDT involves the administration of an inactive photosensitizing agent that, when exposed to light of the proper wavelength, results in oxygen radical production and tissue destruction. Results of a phase III multicenter study that randomized 208 patients on a two to one basis to either PDT plus omeprazole or omeprazole alone demonstrated improved eradication of high-grade dysplasia in the PDT arm (77% versus 39%; $p < 0.0001$) at a 24-month follow-up.[187] A marked reduction in the occurrence of adenocarcinoma was noted in the PDT-treated group (13% versus 28%); however, the results emphasize the risk of development of invasive cancer in a relatively short follow-up interval of 24 months. These results highlight the limitations of PDT, and due to the complexity of treatment and inconvenience of exposure to photosensitizing agents, PDT has fallen out of favor. Limited experience with thermal ablation for high-grade dysplasia has been reported. Small series of either laser ablation[188–189] or argon plasma coagulation[190,191] of high-grade dysplasia suggest that high-grade dysplasia can be eradicated; however, the follow-up period in these studies was short, and invasive carcinoma has subsequently been documented. Radiofrequency ablation is now considered the preferred ablation technique. A randomized trial in 127 patients with Barrett's esophagus and either low- or high-grade dysplasia assigned patients to either a sham endoscopic procedure or to treatment with radiofrequency ablation.[192] Patients assigned to receive radiofrequency ablation were treated with a circumferential ablation device employing an inflatable cylindrical balloon, bringing electrodes into contact with the esophageal lining, with four applications performed per session, and up to four sessions performed over 9 months. At 12 months, a complete eradication of metaplasia occurred in 77.4% of the radiofrequency ablation patients compared to 2.3% in the control group. Although the development of cancer in either group was uncommon, progression to cancer in the ablation group was significantly less in the control group. More long-term follow-up beyond the 12 months in this trial as well as other confirmatory studies are required.

Endoscopic Mucosal Resection

Endoscopic mucosal resection (EMR) is now considered an essential diagnostic, staging, and therapeutic option available for patients with either high-grade dysplasia or superficial esophageal cancers (T1a). The EMR technique either involves a submucosal injection of fluid to lift and separate the lesion from the underlying muscular layer or the use of suction to trap the lesion into a cylinder, which allows for a full resection and tissue retrieval with a snare or endoscopic knife for appropriate histologic examination. Ell et al.[193] prospectively examined the utility of endoscopic resection in 100 consecutive patients with low-risk adenocarcinoma (no ulceration, mucosal lesion, no vascular or lymphatic invasion, less than 20 mm, and not poorly differentiated). Complete local remission was achieved in 99 of 100 patients; at a median follow-up of 33 months, 11% of patients developed recurrent or metachronous carcinomas, all successfully treated with repeat endoscopic resection. The calculated 5-year survival rate was 98% and no patient died of esophageal cancer. In a previous study from the same group,[194] the complete remission rate in patients with less favorable lesions was 59%, which emphasizes the need to adhere to strict criteria to optimize disease eradication.

۰۲۱-۶۶۱۹۸۵۱۴ www.myuptodate.com دریافت آخرین نسخه آپتودیت آفلاین

A report examining the value of EUS and EUS-guided FNA in patients with high-grade dysplasia or intramucosal cancer considered candidates for endoscopic therapy and demonstrated that 20% of patients had unsuspected lymph node metastases and were therefore deemed unsuitable for endoscopic intervention.[195] These results and similar findings in smaller series examining EMR[196,197] confirm that use of this technique is feasible for the treatment of high-grade dysplasia and carcinoma limited to the mucosa (T1a) and provides an alternative to esophagectomy. Furthermore, one could justifiably conclude that patients carefully screened and confirmed to have mucosa-limited lesions should first be offered EMR prior to considering an esophagectomy.[198,199]

Minimally Invasive Esophagectomy

In an attempt to reduce morbidity and mortality while achieving an equivalent oncologic outcome, minimally invasive techniques for esophageal resection have been designed and continue to be investigated. A variety of minimally invasive approaches have been used for esophagectomies, including laparoscopic, thoracoscopic, combined laparoscopic and thoracoscopic, and hand-assisted techniques and robotic assisted.[200–204] These techniques have been described and are similar in conduct to open procedures of transthoracic and transhiatal esophagectomy (detailed in Surgical Resection) except for the nuances of the minimally invasive approach (Figs. 45.8 and 45.9). These procedures have been applied to the treatment of all stages of potentially resectable esophageal cancer, but until oncologic equivalency to open techniques is confirmed, it would seem to be most applicable in the management of premalignant and early-stage disease.

By far the largest single-institution experience with minimally invasive esophagectomies (MIE) has been reported by Luketich et al.,[205] which included 1,011 consecutive patients, the vast majority (95%) of whom had malignant disease. Approximately equivalent numbers of patients underwent either a three-incision MIE or, more recently, an Ivor Lewis MIE. The median intensive care unit stay was 2 days, the median length of hospital stay was 8 days, 30-day perioperative mortality was 1.7%, and the R0 resection rate was 98%. Median follow-up was only 20 months, and stage-specific survival was similar to that reported in a series with open esophagectomies. This group concluded that MIEs are safe and an appropriate surgical approach in experienced hands. The same group reported their experience with 100 consecutive patients with T1 esophageal cancer who underwent esophagectomy, 80% of which were performed via a minimally invasive approach. The 30-day mortality was 0% and a R0 resection was achieved in 99%. N1 disease was present in 21% of patients, the majority of whom (90%) had T1b lesions with submucosal invasion. At a median follow-up of 5.5 years, 5-year overall survival was 62% and 3-year disease-free survival was 80%. The authors concluded that esophagectomies remain the standard of care for patients with T1 esophageal cancer.[206] The results following minimally invasive esophagectomies reported by this group at the University of Pittsburgh are both promising and impressive, but whether they are reproducible in other institutions and therefore more broadly applicable needed to be determined through further study.[207,208] The first, multicenter, randomized controlled trial of MIEs versus open esophagectomies recently reported its short-term results. Patients (n = 115) were randomly assigned to MIEs or open esophagectomies with the primary endpoint of postoperative pulmonary infection within 2 weeks of surgery. MIEs were associated with a statistically significant reduction in pulmonary infections and in length of stay. There was no difference detected in either 30-day or in-hospital mortality, and postoperative complication rates were similar. Patients randomized to the MIE arm had statistically significant longer operative times and decreased operative blood loss. Long-term oncologic outcomes are pending, but R0 resection rates and lymph node retrieval were equivalent between minimally invasive and open approaches.[209]

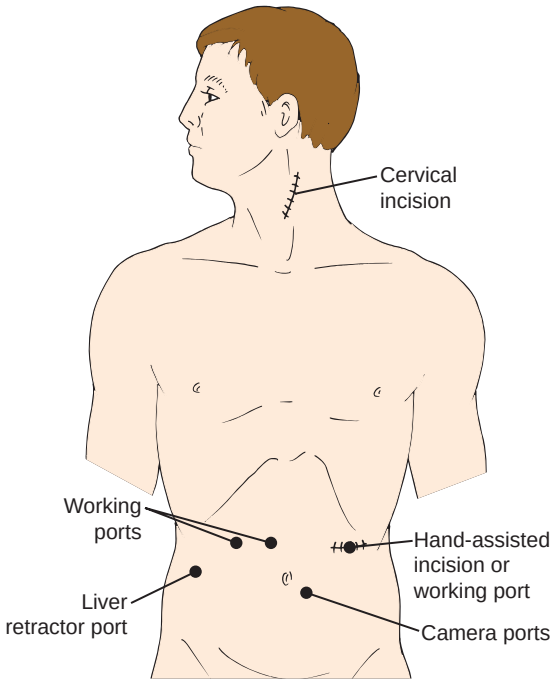

Figure 45.8 Abdominal port sites and incisions used for minimally invasive esophagectomy.

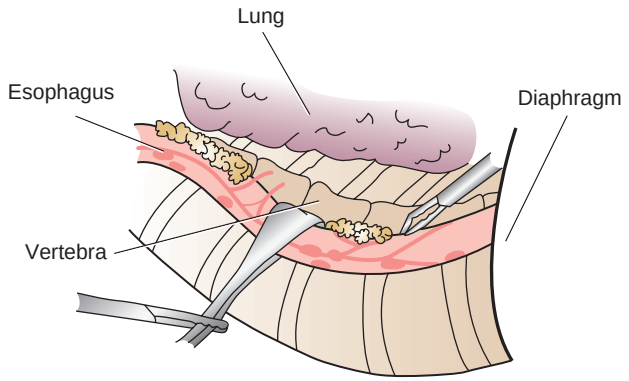

Figure 45.9 Thoracoscopic view and dissection of intrathoracic esophagus.

Nonresection or Ablative Therapy

There is limited experience with the use of radiation or chemoradiation in the curative setting for patients with cT1N0 disease. Sai et al.[210] from Kyoto University treated 34 patients who were either medically inoperable or refused surgery with either external beam alone (64 Gy) or external beam (52 Gy) plus 8 to 12 Gy with brachytherapy. With a median follow-up of 61 months, 5-year results were 59% survival, 68% local relapse-free survival, and 80% cause-specific survival. Treating a similar population of 63 patients with chemoradiation plus brachytherapy, Yamada et al.[211] reported 66% survival, 64% disease-free survival, and 76% cause-specific survival at 5 years. In a recent cohort study of patients with clinical stage T1bN0 esophageal squamous cell carcinoma of the thoracic esophagus, nearly 20% of patients in the surgery cohort of 102 patients had nodal involvement on pathologic inspection. Patients who received definitive chemoradiotherapy (n = 71) had a higher risk of disease recurrence. Local recurrence in the definitive chemoradiotherapy cohort could be controlled by salvage esophagectomy

۰۲۱-۶۶۱۹۸۵۱۴ www.myuptodate.com tahir99 - UnitedVRG دریافت آخرین نسخه آپتودیت آفلاین

30% of the time, with the remaining ultimately dying of progressive esophageal adenocarcinoma.[212] These data highlight the importance of patient selection in the decision process for local–regional therapy for early stage esophageal carcinoma.

Treatment of Localized Disease

Surgery has traditionally been the treatment of choice for patients with localized, resectable carcinoma of the esophagus and continues to be a component of a more comprehensive approach to esophageal cancer in a substantial number of patients. Failure of surgery alone to significantly alter the natural history of esophageal cancer has resulted in considerable and appropriate enthusiasm for multimodality therapy approaches. The shift toward multimodal treatment is not only theoretically sound, but is also supported by results from phase III randomized trials. Recent trials, unlike their predecessors, which were statistically underpowered and often came to conflicting conclusions about the worth of preoperative therapeutic regimens (radiation, chemotherapy, or chemoradiation), consistently demonstrate benefit to neoadjuvant therapy compared to surgery alone. Results from clinical trials have also brought into question the role of surgery in a multimodal approach to treatment of esophageal cancer, with studies (almost exclusively in squamous cell cancer) suggesting the absence of a survival benefit for the addition of surgery after chemoradiation, despite improved local disease control. Most clinicians and investigators consider some form of combined modality treatment that includes surgery to be the standard of care for localized, resectable esophageal cancer.

Surgical Resection

Decisions regarding surgical technique are routinely based on personal bias, comfort level of the surgeon, and a subjective view of tumor biology because solid evidence from scientifically designed trials is nonexistent. Studies that used health services–linked databases have demonstrated a statistically significant association between performance of surgery in hospitals designated as high-volume esophagectomy institutions with lower complication and mortality rates.[214–217] A study from the Netherlands noted a significant reduction in postoperative morbidity, decrease in length of stay, reduction in in-hospital mortality, and improved 2-year survival following centralization of esophageal resections in high volume units when compared to before the centralization project was introduced.[218] Importantly, the strength of the inverse volume–outcome relationship for esophagectomy has significantly increased over time (2008 to 2009 versus 2000 to 2001) with the adjusted odds ratio of mortality in very low volume hospitals increasing substantially compared to that of very high volume hospitals.[219]

Transhiatal Esophagectomy. The transhiatal route for esophageal resection has gained favor, especially among surgeons in the United States, concurrent with the rising incidence of adenocarcinoma of the distal esophagus, which is readily approachable and effectively dissected through the diaphragmatic hiatus (Table 45.3). The technique is as follows.[220,221] It is prudent to initially perform laparoscopic exploration to rule out disseminated disease and, if it is confirmed, to abort the intended resection before exposing the patient to the risks of laparotomy. Through a midline incision, the stomach is mobilized by dividing all vascular attachments while preserving the right gastroepiploic and right gastric vessels on whose pedicle the reconstructive conduit will be based. The duodenum is fully mobilized via a Kocher maneuver and a pyloric drainage procedure is performed, which has been demonstrated in prospective randomized trials to reduce gastric stasis and minimize pulmonary complications such as aspiration.[222,223] Cautery division of the diaphragmatic crus allows for wide access to the mediastinum and dissection under direct vision of the middle and lower third of the esophagus. A left cervical incision provides exposure to the cervical esophagus, and circumferential dissection of the cervical esophagus is carried down to below the thoracic inlet to the upper thoracic esophagus, with care to avoid injury to the recurrent laryngeal nerve. The remainder of the dissection at the level of and superior to the carina is completed by blunt dissection through the esophageal hiatus.

The cervical esophagus is then divided, the stomach and attached intrathoracic esophagus are delivered through the abdominal wound, and a gastric tube, which will serve as the reconstructive conduit, is fashioned using multiple applications of a linear stapling device. The gastric tube is then transposed through the posterior mediastinum to the cervical wound, where a cervical esophagogastric anastomosis is performed. The stomach is considered by most surgeons as the replacement conduit of choice for the resected esophagus. A segment of colon, usually based on the ascending branch of the inferior mesenteric artery, is an effective esophageal substitute if for any reason the stomach is deemed unsuitable for reconstruction or if it is the surgeon's preference. Although the original intent of this approach was not to perform a methodical lymph node dissection, a standard two-field lymphadenectomy (abdominal and lower mediastinal) can readily be achieved, and for that matter, if the surgeon is so inclined, a radical en bloc resection can be performed, as described by Bumm et al.[224]

The stated advantages attributed to the transhiatal approach to esophagectomy include avoidance of a thoracotomy incision, which thereby minimizes pain and subsequent postoperative pulmonary complications; elimination of the lethal complications of mediastinitis associated with an intrathoracic anastomotic leak; and a shorter duration of operation, which results in decreased morbidity and mortality.[221] Limitations and disadvantages of transhiatal esophagectomy include poor visualization of upper and middle thoracic esophageal tumors, increased anastomotic leak rate with subsequent stricture formation, the possibility of chylothorax, and the possibility of recurrent laryngeal nerve injury. The largest experience with transhiatal esophagectomy was reported by Orringer et al.[225] and included 1,525 patients with esophageal

TABLE 45.3

Conventional Approaches to Esophageal Resection for Cancer

Transhiatal
- Laparotomy and cervical approach
- Peritumoral or two-field lymph node dissection
- En bloc resection feasible for distal esophageal tumors
- Cervical anastomosis

Transthoracic
- Ivor Lewis
  - Right thoracotomy and laparotomy
  - Peritumoral or two-field lymph node dissection
  - En bloc resection feasible for middle/distal thoracic tumors
- McKeown or "three hole"
  - Right thoracotomy, laparotomy, cervical approach
  - Peritumoral, two-field or three-field lymph node dissection
  - En bloc resection feasible for mid- or distal thoracic tumors
  - Cervical anastomosis
- Left thoracotomy
  - Left thoracotomy with or without cervical approach
  - Peritumoral lymph nodes dissection
  - Intrathoracic or cervical anastomosis
- Left thoracoabdominal
  - Left thoracoabdominal approach
  - Peritumoral or two-field lymph node dissection
  - Intrathoracic anastomosis

۰۲۱-۶۶۱۹۸۵۱۴ www.myuptodate.com دریافت آخرین نسخه آپتودیت آفلاین

TABLE 45.4

Results of Transhiatal Esophagectomy for Esophageal Cancer

Study (Ref.)	Year	No. of Patients (n)	Histologic Type	Perioperative Mortality (%)	5-Year Survival (%)
Gelfand et al.[227]	1992	160	A	0.9	21
Gertsch et al.[229]	1993	100	A/S	3	23
Vigneswaran et al.[228]	1993	131	A/S	2.3	21
Dudhat and Shinde[231]	1998	80	S	7.5	37
Orringer et al.[226]	1999	800	A/S	4.5	23
Bolton and Teng[230]	2002	124	A/S	1.6	27.3

A, adenocarcinoma; S, squamous cell carcinoma.

cancer, 79% of whom had adenocarcinoma and 21% of whom had squamous cell carcinoma. Tumors were located in the lower third of the esophagus in 82% and in the middle or upper third in 18%. In-hospital mortality was 3%. The most common complications were anastomotic leak (12%) and recurrent laryngeal nerve palsy (4.5%). Leak of a cervical esophageal gastric anastomosis was handled simply, in most patients with opening of the cervical wound, followed by local wound care. Hoarseness from recurrent laryngeal nerve injury resolved spontaneously in 99% of cases. Overall 5-year survival was 29%, and stage-specific 5-year survival was 65% for stage I, 28% for stage II, 29% for stage IIB, and 11% for stage III. These results reflect those reported from other surgical series of transhiatal esophagectomy (Table 45.4).[226–231]

Transthoracic Esophagectomy. The transthoracic esophagectomy has been the most common surgical approach used to resect carcinomas of the esophagus and is the standard procedure against which all other techniques are measured (see Table 45.3). Although a left thoracotomy provides adequate exposure to tumors of the distal esophagus, a right thoracotomy affords access to upper, middle, and distal esophageal lesions and is the preferred route for transthoracic exposure. A right thoracotomy combined with an upper midline laparotomy (Ivor Lewis esophagectomy) is the technique most commonly used for esophageal resection and is briefly described here.[221] The abdominal portion of the procedure duplicates that of the transhiatal approach previously detailed and includes mobilization of the stomach and distal esophagus, upper abdominal lymphadenectomy, pyloromyotomy, and placement of a feeding jejunostomy before abdominal wound closure and repositioning for the thoracic component of the procedure. A muscle-sparing right lateral thoracotomy is performed through the fifth or sixth intercostal space. The azygos vein is divided, the mediastinal pleura incised, the intrathoracic esophagus mobilized, and a mediastinal lymph node dissection performed.

After division of the proximal esophagus in the chest to ensure an adequate margin, the GEJ and stomach are pulled into the thoracic cavity. The stomach is then divided with a linear stapler, the specimen is removed, and an esophagogastric anastomosis is performed. An alternative approach has been described in which the right thoracotomy is the initial stage of the procedure followed by repositioning of the patient supine for an abdominal and left cervical incision to achieve a cervical esophagogastric anastomosis.[232,233] Initial experience with a minimally invasive Ivor Lewis esophagectomy has also been reported.[234]

The transthoracic approach provides direct visualization and exposure of the intrathoracic esophagus, facilitating a wider dissection to achieve a more adequate radial margin around the primary tumor and more thorough lymph node dissection, which theoretically results in a more sound cancer operation. In patients with significant comorbid conditions, the combined effects of an abdominal and thoracic incision may compromise cardiorespiratory function. An intrathoracic anastomotic leak can lead to mediastinitis, sepsis, and death. In addition, esophagitis in the nonresected thoracic esophagus may occur secondary to bile reflux. The three-incision (cervical, thoracic, and abdominal) modification of the procedure effectively eliminates the potential for complications associated with an intrathoracic esophagogastric anastomosis.

Numerous authors have reported results of transthoracic esophagectomy; however, most, if not all, of these reports include patients who were resected via other surgical approaches and underwent a more extended lymphadenectomy (Table 45.5).[235–240] Both overall and stage-specific 5-year survival rates were similar to those seen with a transhiatal esophagectomy. The most reliable data may be derived from prospective randomized trials in which there is a surgery-alone control arm. In only one of those trials[240] was a transthoracic approach the only surgical procedure allowed. In that trial, median survival time on the surgery alone arm was 18.6 months and 5-year survival rate was 26%.

TABLE 45.5

Results of Transthoracic Esophagectomy for Esophageal Cancer

Study (Ref.)	Year	No. of Patients (n)	Histologic Type	Perioperative Mortality (%)	5-Year Survival (%)
Wang et al.[238]	1992	368	S	6.5	7.6
Lieberman et al.[239]	1995	258	A/S	5	27
Adam et al.[237]	1996	597	A/S	6.9	16.3
Sharpe and Moghissi[235]	1996	562	A/S	9	18
Bosset et al.[240]	1997	139	S	3.6	26
Ellis[236]	1999	455	A/S	3.3	24.7

A, adenocarcinoma; S, squamous cell carcinoma.

۰۲۱-۶۶۱۹۸۵۱۴ www.myuptodate.com tahir99 - UnitedVRG دریافت آخرین نسخه آپتودیت آفلاین

Transhiatal Versus Transthoracic Esophagectomy. The controversy regarding the optimal surgical approach for esophageal cancer remains unresolved. Two large meta-analyses have compared transhiatal esophagectomy with transthoracic esophagectomy based on collective reviews of numerous individual studies.[241,242] Both reports include studies that compared transhiatal with transthoracic esophagectomies, studies of transhiatal esophagectomies only, and studies of transthoracic esophagectomies only. Rindani et al.[241] reviewed 5,483 patients from 44 series published between 1986 and 1996. Perioperative mortality was significantly higher in the transthoracic esophagectomy group than in the transhiatal group (9.5% versus 6.3%), whereas overall perioperative complications were not significantly different. Transhiatal esophagectomies resulted in a higher incidence of anastomotic leak, anastomotic stricture, and recurrent laryngeal nerve injury. Overall 5-year survival was similar: 24% for transhiatal esophagectomies and 26% for transthoracic esophagectomies. Hulscher et al.[242] performed a collective review of 50 studies performed between 1990 and 1999 yielding 7,527 patients. Postoperative mortality was significantly greater in the transthoracic group than in transhiatal group (9.2% versus 5.7%). Transthoracic esophagectomies were associated with a significantly higher risk of pulmonary complications (18.7% versus 12.7%), whereas patients treated with a transhiatal esophagectomy had a higher anastomotic leak rate (13.6% versus 7.2%). Five-year survival was not significantly different, with a 23% 5-year survival for transthoracic and a 21.7% 5-year survival with transhiatal esophagectomies. A third meta-analysis of over 50 comparative studies with a total of 5,905 patients included studies published up to 2010 and also included the largest randomized controlled trial. In-hospital or 30-day mortality was significantly higher in the transthoracic group (10.6% versus 7.2%) as was pulmonary complications and length of stay (4 days greater). Anastomotic leak (16.9% versus 10.6%), anastomotic stricture and vocal cord paralysis was significantly higher in the transhiatal group. Five-year overall survival was not statistically different between the transthoracic (26.6%) and transhiatal (25.8%) groups.[243] A prospective database based on the Veterans Administration National Surgical Quality Improvement Program analyzed perioperative outcome in 945 patients: 562 who underwent transthoracic esophagectomy and 383 who underwent resection through a transhiatal approach.[244] There was no difference in overall mortality (10% for transthoracic approach versus 9.9% for transhiatal approach) or morbidity (47% for transthoracic versus 49% for transhiatal). A large population-based study evaluated transhiatal and transthoracic esophagectomies through the SEER Medicare-linked database from 1992 to 2002.[245] A lower operative mortality was found after transhiatal esophagectomies (6.7% versus 13.1%). Although observed 5-year survival was higher after a transhiatal esophagectomy, after adjusting for stage, patient, and provider factors, no significant 5-year survival difference was found.

Four phase III trials have prospectively examined the outcomes for patients randomly assigned to undergo either a transhiatal or a transthoracic esophagectomy.[246–249] No definitive conclusions can be drawn from three of these trials because of the extremely small sample size. The trial in the Netherlands, however, deserves special attention. Hulscher et al.[249] randomly assigned 220 patients with middle or distal esophageal carcinoma to undergo either a transhiatal esophagectomy or a transthoracic esophagectomy. The transthoracic group underwent a systematic mediastinal and upper abdominal lymph node dissection. Although the number of lymph nodes retrieved was significantly higher in the transthoracic group (31 versus 16; $p < 0.001$), there was no difference in the radicality of the two procedures with equivalent R0, R1, and R2 resections. Postoperative pulmonary complications, ventilatory time, intensive care unit stay, and hospital stay were significantly higher in those patients assigned to the transthoracic group. Despite the higher perioperative morbidity, there was no statistically significant increase in in-hospital mortality (4% versus 2% for transthoracic versus transhiatal esophagectomy, respectively; $p = 0.45$). At a median follow-up of 4.7 years, there were no significant differences between the transhiatal and transthoracic esophagectomy groups with respect to median disease-free interval (1.4 years versus 1.7 years) and median overall survival time (1.8 years versus 2.0 years), respectively. Likewise, no significant differences were noted in local–regional recurrence, distant recurrence, and combined local–regional and distant recurrence for patients randomly allocated to the transthoracic or transhiatal esophagectomy arm. The investigators point out that a trend toward improved disease-free survival (39% versus 27%) and overall survival (39% versus 29%) at 5 years favored the transthoracic approach group. However, a recent update on this study that provided complete 5-year survival data demonstrated that survival was equivalent in patients randomized to either a transhiatal (34%) or transthoracic (36%) resection.[250]

Either the transhiatal or transthoracic procedure can be performed with acceptable morbidity and mortality in experienced hands and, with either technique, the outcome is remarkably similar.

Extended Esophagectomy. In an attempt to improve on the dismal results reflected in high local recurrence rates and poor overall survival with standard transhiatal and transthoracic esophagectomy techniques, some surgeons have examined extending the limits of resection to accomplish a more effective primary tumor excision and lymph node dissection. Two concepts guide the intent of these more extended resections: en bloc resection of the primary tumor with its adjacent surrounding tissue and systematic lymph node dissection, encompassing either two (mediastinal and abdominal) or three (cervical, mediastinal, and abdominal) lymph node basins (Fig. 45.10). Although some investigators have focused and reported separately on en bloc esophagectomies and extended lymphadenectomies, most of the techniques described encompass both components of this "radical" approach. An en bloc esophagectomy involves the resection of middle and lower esophageal tumors with an envelope of adjacent tissue that includes the mediastinal pleura laterally, the pericardium anteriorly, and the azygos vein and thoracic duct posterolaterally with the surrounding periesophageal tissue and lymph nodes. For tumors traversing the esophageal hiatus, a cuff of diaphragm is resected. In addition to a thorough mediastinal lymph node dissection extending from the tracheal bifurcation to the esophageal hiatus, an upper abdominal lymph node dissection incorporating lymph nodes along the portal vein, common hepatic artery, celiac trunk, left gastric artery, and splenic artery is included to achieve a two-field lymph node dissection.[251] A three-field lymph node dissection extends the lymphadenectomy to the superior mediastinum, including nodes along the course of the right and left recurrent laryngeal nerves, and, through a separate collar incision in the neck, completes the dissection with removal of the lower cervical nodes, including the deep external and lateral cervical lymph node basins.[96,97]

Most of the series that examine the utility of extended esophagectomies are retrospective and involve a single institution. Hagen et al.[91] reported on 100 consecutively treated patients who had undergone an en bloc esophagectomy with two-field lymphadenectomies; none of the patients received additional preoperative or postoperative chemotherapy or radiotherapy. The perioperative mortality was 6%, with the most common complications being pneumonia (19%), subphrenic abscess (13%), respiratory failure (9%), anastomotic leak (10%), and empyema (7%). Local recurrence was detected in only one patient and overall actuarial 5-year survival was 52%. Patients with stage III lesions had a 25% actuarial 5-year survival. Altorki et al.[92] reviewed the results for 128 patients who underwent an esophagectomy at a single institution; 61% received an en bloc esophagectomy and the remainder underwent a standard esophageal resection. Approximately 40% of those undergoing the more extended resection had a three-field lymphadenectomy; the others had a systematic two-field lymphadenectomy. The in-hospital mortality for the en bloc resection

۰۲۱-۶۶۱۹۸۵۱۴ www.myuptodate.com دریافت آخرین نسخه آپتودیت آفلاین

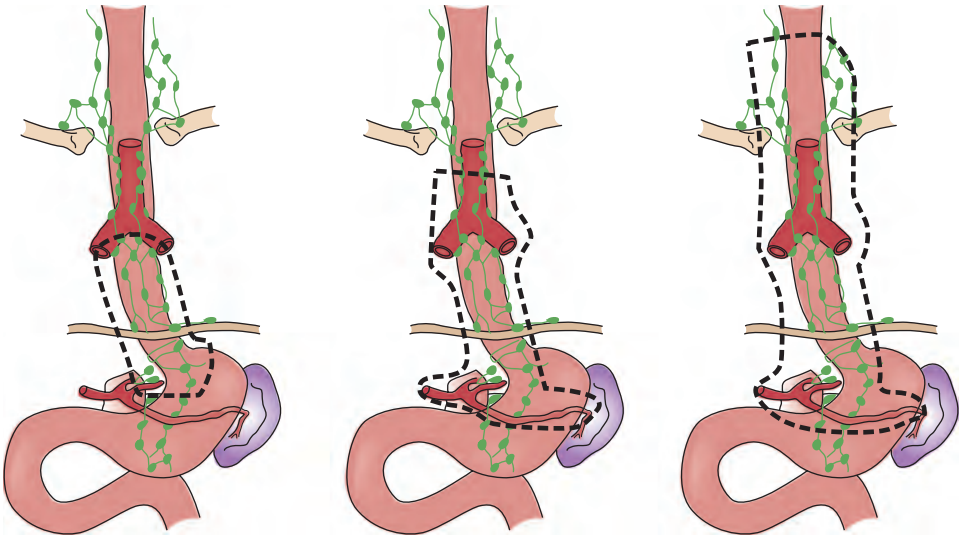

Figure 45.10 *Left to right:* Standard, two-field, and three-field lymphadenectomy.

group was 5.1%, similar to that for those undergoing a standard resection. The most common postoperative complications in the extended resection group were respiratory events (24%) and anastomotic leak (12.8%), but no significant differences were noted in comparison to the standard resection group. Four-year survival for the en bloc group was 41.5% overall and 34.5% for stage III patients, with both of these survival figures markedly better than those for the standard resection group. However, both of the studies described here are single-institution, retrospective analyses for which the results, at least in part, if not completely, can be attributed to selection bias and enhanced staging, leading to stage migration. It is interesting to note that similar results have been achieved without a thoracotomy using a transhiatal approach as described earlier in Transhiatal Esophagectomy.[224]

A group at Cornell University also separately examined 80 patients who underwent an esophagectomy with a three-field lymphadenectomy.[94] Overall 30-day mortality was 5%, with 31% of patients developing major postoperative complications, including the need for reintubation (16%), anastomotic leak (11%), and recurrent laryngeal nerve injury (9%). Overall 5-year survival was 51%. Cervical lymph node metastases were identified in 36% of patients, and the 5-year survival rate for those with positive cervical lymph nodes was 25%. Lerut et al.[252] reported on 174 patients, equally divided between squamous cell and adenocarcinoma histology, who underwent a three-field lymphadenectomy. Hospital mortality was only 1.2%, with an overall mortality of 58%. Five-year survival for stage III patients was 36.8%. Twenty-three percent of patients with adenocarcinoma and 25% of those with squamous cell carcinoma had positive cervical nodes. Five-year survival for patients with positive cervical lymph nodes was 27% and 12%, respectively, for squamous cell and adenocarcinoma histology. The authors suggest that a three-field lymphadenectomy may have a role in patients with squamous cell carcinoma, but this remains investigational for patients with adenocarcinoma. These results, although impressive, may also reflect both selection bias and stage migration. In addition, the expertise required to perform these technically demanding procedures effectively limits their application to specialized centers only and a fraction of the patients who might benefit from these procedures if an actual advantage were proven.

The Hulscher trial, discussed previously, which also employed an en bloc resection of the esophagus, compared to transhiatal esophagectomies, failed to improve outcome.[250] A small study by Nishihira et al.[253] of 62 patients showed an improved, but not statistically significant, survival advantage for extended lymphadenectomies (66.2% versus 48%; $p = 0.19$). Patients in this study were also randomly assigned to receive either chemoradiation or chemotherapy alone after surgery, confounding the interpretation of the results.

The body of evidence confirms that extended resections improve staging and may enhance local–regional control; however, there are no reliable data confirming a survival benefit for these procedures.

Adjuvant Therapy

Preoperative Chemotherapy. Nearly three-fourths of patients newly diagnosed with esophageal cancer present with locally advanced (stage IIB or III) disease. The poor survival rate achieved with surgery alone, and given the patterns of both local and systemic disease recurrence, has provided the impetus for the evaluation of preoperative (induction) chemotherapy in patients with resectable esophageal cancer.

The benefits of induction chemotherapy include the potential downstaging of the disease to facilitate surgical resection, improvement in local control, relief of dysphagia in patients responding to induction chemotherapy, and the potential eradication of micrometastatic disease. An esophagectomy after induction therapy enables a comprehensive pathologic assessment of treatment response, which may be important in selecting patients for postoperative adjuvant therapy. The disadvantages of preoperative chemotherapy include the potential development of chemotherapy resistance and the delay in definitive treatment with the risk of further spread of the disease. These are important concerns because approximately 50% of patients do not respond to current chemotherapeutic regimens. Further compromise of the patient's already marginal nutritional status due to a delay in local disease control is also of concern when surgery is not the initial treatment.

Trials evaluating the use of induction chemotherapy followed by surgery for the treatment of esophageal cancer have been under way since the late 1970s. This strategy was evaluated in parallel with studies of concurrent chemoradiation followed by surgery or chemoradiation as definitive therapy. Early trials used cisplatin and bleomycin-based chemotherapy.[254–257] Use of cisplatin and 5-fluorouracil (5-FU)[258–262] led to the initiation of randomized trials in the 1980s. For lesions of squamous histology, the response rate to two or three cycles of cisplatin (100 mg/m^2 on day 1) and 5-FU (1,000 mg/m^2 per day for 96 or 120 hours) every 3 weeks ranged between 42% and 66%, with a 0% to 10% pathologically confirmed complete-response rate; curative resection rates were between 40% and 80%, and median survival was from 18 to 28 months.[258–262] Lesions were staged with a barium esophagogram and CT scan initially and then again before surgery to assess the response to induction therapy.

۰۲۱-۶۶۱۹۸۵۱۴ www.myuptodate.com tahir99 - UnitedVRG دریافت آخرین نسخه آپتودیت آفلاین

TABLE 45.6

Randomized Trials of Preoperative Chemotherapy

Study (Ref.)	Treatment	No. of Patients (n)	Histologic Type	Median Survival (months)	3- or 5-Year Survival (%)
Nygaard et al.[263]	Preop C/B Surgery	50 41	S		3 yr: 3 3 yr: 9
Roth et al.[264]	Preop C/VDS/B and adjuvant C/VDS Surgery	19 20	S	9 9	5 yr: 25 5 yr: 5
Schlag[265]	Preop C/5-FU Surgery	34 41	S	10 10	NS NS
Boonstra et al.[269]	Preop C/etoposide Surgery	86 85	S	16 12	5 yr: 26 5 yr: 17
Kelsen et al. (Intergroup 0013)[105,112]	Preop C/5-FU and adjuvant C/5-FU Surgery	213 227	S/A	15 16	3 yr: 26 3 yr: 23
Allum et al.[106,113]	Preop C/5-FU Surgery	400 402	S/A A	16.8 13.3	5 yr: 23 5 yr: 17
Cunningham et al.[266]	Preop/postop ECF Surgery	250 253	A A	24 20	5 yr: 36 5 yr: 23
Ychou et al.[267]	Preop/postop CF Surgery	113 111	A A	— —	5 yr: 38 5 yr: 24
Schuhmacher et al.[268]	Preop CF Surgery	72 72	A A	65 53	— —

Preop, preoperative; C, cisplatin; B, bleomycin; VDS, vindesine; S, squamous cell carcinoma; A, adenocarcinoma; ECF, epirubicin/cisplatin; 5-FU, 5-fluorouracil; postop, postoperative.

Nine randomized trials evaluating the use of preoperative chemotherapy in esophageal cancer patients are summarized in Table 45.6.[105,106,263–269] Four of the trials enrolled only patients with squamous cell carcinoma,[263–265,267–269] whereas half to two-thirds of patients enrolled in the two more recent and largest trials (U.S. Intergroup and Medical Research Council) had adenocarcinoma of the esophagus, GEJ, or cardia.[105,106] Another large randomized trial treated mostly gastric cancer, although one-fourth of patients enrolled had adenocarcinoma of the distal esophagus or GEJ.[266] Two recent small European trials treated only adenocarcinoma of the esophagus and stomach with half or more of patients having esophageal or GEJ adenocarcinoma.[267,268]

No improvement in survival was noted in three small trials enrolling fewer than 100 patients each, with the small sample size making study interpretation difficult.[263–266] Boonstra et al.[269] reported a survival advantage for preoperative chemotherapy in the final report of a study initially published in abstract form back in 1997. This study, enrolling 171 patients with squamous cell carcinoma, differed from other trials by requiring a response assessment after two courses of preoperative chemotherapy. Patients showing no response underwent immediate surgery, whereas patients showing a response received two more courses of chemotherapy before surgery. The regimen consisted of cisplatin (80 mg/m^2 on day 1) and etoposide (100 mg/m^2 intravenously on days 1 to 2 and 200 mg/m^2 orally on days 3 to 5). Median overall survival in the surgery arm was 12 months compared to 16 months for surgery plus chemotherapy. Fewer patients went on to surgery after preoperative chemotherapy (89%) compared to patients undergoing immediate surgery (97%). Rates of R0 resection favored the chemotherapy arm, but the difference was nonsignificant ($p = 0.09$). Overall survival was superior with preoperative chemotherapy (hazard ratio [HR], 0.71; $p = 0.03$) with the 5-year survival for chemotherapy plus surgery 26% compared to 17% for surgery alone.

The U.S. Intergroup mounted a large, potentially definitive trial, INT-0113. A total of 467 patients with resectable esophageal cancer were randomly assigned to one of two treatment groups: (1) three cycles of cisplatin and 5-FU followed by surgery and then, for those patients whose resection was curative (R0), two additional cycles of cisplatin and 5-FU as adjuvant treatment; or (2) immediate surgery.[105] In contrast to other trials, a barium esophagogram was the only test required to assess clinical response to preoperative chemotherapy. Thus, it is not surprising that only a 19% response rate was reported. Survival and pattern of failure were the major study end points. No differences were observed between the surgery control group and the preoperative cisplatin and 5-FU group in terms of curative resection rate (59% versus 62%), treatment mortality (6% versus 7%), overall median survival (16.1 months versus 14.9 months), or 3-year survival (26% versus 23%) (Fig. 45.11). Furthermore, the median survival of patients who had a curative resection was the same in both treatment groups (27.4 months versus 25.0 months). The pattern of failure was also similar for the two treatment groups (local recurrence 31% versus 32%, and distant recurrence of 50% versus 41% in the surgery-alone group compared to those receiving induction chemotherapy followed by surgery, respectively). Tumor histologic type did not influence response to treatment. A recent update of the trial reported no late benefit for preoperative chemotherapy.[112] The importance of achieving an R0 resection in the updated analysis was emphasized, with these patients achieving long-term survival, whereas patients with an R1 resection treated only with surgery all died of recurrent disease. The only patients with R1 resection achieving long-term survival were those receiving protocol-permitted postoperative chemoradiotherapy: Among 34 patients treated with surgery alone with R1 resection, 18 received postoperative chemoradiotherapy and 9 (21%) achieved long-term survival. These results indicated that R1 resection patients may be salvaged with postoperative chemoradiotherapy.

۰۲۱-۶۶۱۹۸۵۱۴ www.myuptodate.com دریافت آخرین نسخه آپتودیت آفلاین

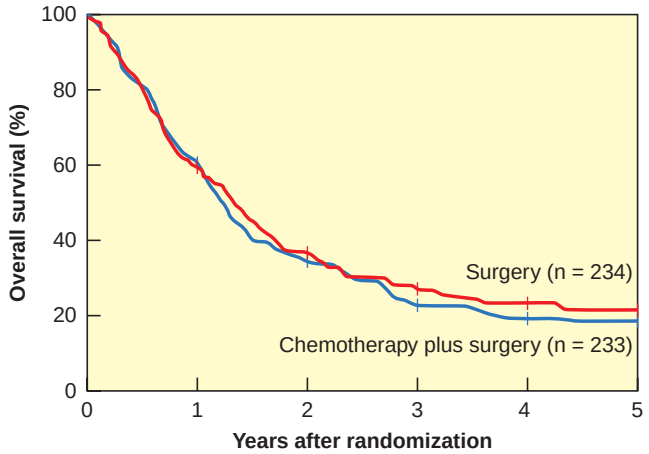

Figure 45.11 Overall survival US Intergroup trial INT-0113 comparing patients randomized to preoperative chemotherapy versus surgery alone.

Although no improvement in survival was demonstrated for preoperative chemotherapy on INT-0113, the trial importantly provides a contemporary surgical experience in the treatment of esophageal squamous carcinoma and adenocarcinoma. Important outcomes in this trial include a postoperative death rate well below 10%, the lack of difference in survival for lesions of different histologic types, and the fact that an R0 curative resection (regardless of treatment) conferred a median survival time of more than 2 years.

In contrast to the results of the 467-patient U.S. Intergroup trial, the Medical Research Council (MRC) Oesophageal Cancer Working Group demonstrated a statistically significant 9% improvement in 2-year survival rate (43% versus 34%) (Fig. 45.12) with preoperative cisplatin and 5-FU.[106] A total of 802 patients, 31% with squamous lesions and 69% with adenocarcinoma or lesions of undifferentiated histologic type, were enrolled. Patients were randomly assigned either to receive two courses of cisplatin (80 mg/m^2) and 5-FU (1,000 mg/m^2 per day, continuous infusion for 4 days) 3 weeks apart followed by surgery or to undergo immediate surgery. The curative resection (R0) rate (60% versus 54%) and the percentage of randomly assigned patients undergoing surgery (92% versus 97%) were similar for the two treatment groups, although the improvement in curative resection rate did reach statistical significance. Patients receiving preoperative chemotherapy had improved median survival (16.8 months versus 13.3 months) and 2-year survival rate (43% versus 34%) (Fig. 45.12). Overall survival was significantly improved with preoperative chemotherapy

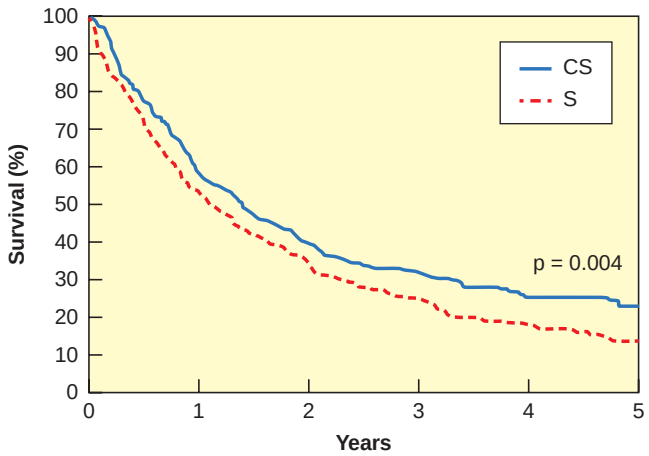

Figure 45.12 Overall survival Medical Research Council (MRC) Oesophageal Cancer Working Group trial comparing patients randomized to preoperative chemotherapy (CS) versus surgery alone (S).

(p = 0.004; HR, 0.79; 95% CI, 0.67 to 0.93). The estimated reduction in risk of death was 21%. The postoperative mortality rate was 10% in both treatment groups. Pathologic complete responses were rare and were reported in 4% of patients undergoing preoperative chemotherapy. These authors recently reported an update of this trial at a median follow-up of 6 years.[113] Although a survival benefit was maintained in the preoperative chemotherapy arm, it had diminished to only 6% at 5 years (23.0% for preoperative therapy versus 17.1% for surgery; HR, 0.84; p = 0.03). There was no difference in pattern of failure—in particular, the development of distant metastatic disease—in the chemotherapy surgery versus surgery alone group, with the authors attributing the survival improvement with preoperative chemotherapy to the enhancement of rate of curative resection. The modest survival improvement with preoperative chemotherapy in this trial update is consistent with a 4.3% survival benefit observed in a recent meta-analysis of preoperative chemotherapy reported in abstract form, in which updated survival data from individual trials were obtained in over 2,000 patients in nine studies.[270]

There is no clear explanation for the discrepancy in survival outcome for the INT and MRC trials, whereas survival of the surgery control groups was essentially the same. The MRC study had the advantage of a larger sample size and greater power to observe a small difference. A greater proportion of patients who received chemotherapy underwent surgery in the MRC study, 92% compared with 80% in the INT trial. Although a microscopically complete resection (R0) was performed in similar proportions in the two trials, the MRC trial indicated a higher rate of R0 resection with preoperative chemotherapy compared to surgery alone. The duration of preoperative chemotherapy in the MRC trial was shorter and may have lessened the risk to patients of disease progression during induction therapy.

Positive results of another recent trial of perioperative chemotherapy in gastric and distal esophagus or GEJ cancer have been reported. In a trial by Cunningham et al.,[266] 503 patients were assigned to three cycles of preoperative and three cycles of postoperative epirubicin/cisplatin/5-FU or surgery alone. Preoperative chemotherapy resulted in significant improvement in patient survival, with a 6-month improvement in progression-free survival, a 4-month improvement in median survival, and a 13% improvement in 5-year overall survival (23% to 36%), all of which are statistically significant. Despite the survival improvement with pre- and postoperative chemotherapy, there was no improvement in the rate of curative resection in patients treated with preoperative chemotherapy compared with surgery alone (66% to 69%), and there were no cases of pathologic complete response to preoperative chemotherapy. Downstaging was also observed with preoperative chemotherapy, with a shift to earlier T and N stage tumors with preoperative chemotherapy compared to surgery alone. Because 26% of patients on this trial had tumors in the GEJ and lower esophagus, the results may apply to locally advanced esophageal cancer. The median follow-up was 47 months in the surgery-alone arm and 49 months in the chemotherapy arm.

Two recent studies from Europe also came to conflicting results for any benefit for preoperative chemotherapy. Ychou and colleagues[267] randomized 234 patients with esophageal, GEJ, or gastric adenocarcinoma to immediate surgery or to perioperative chemotherapy with cisplatin and fluorouracil. Rates of R0 resections were improved with preoperative chemotherapy to 84% compared to 74% for surgery alone (p = 0.04). At a median follow-up of 5.7 years, preoperative chemotherapy improved 5-year survival from 24% to 38%. On the other hand, Schuhmacher and colleagues[268] for the European Organisation for Research and Treatment of Cancer (EORTC) reported a negative trial of 144 patients with GEJ junction or gastric adenocarcinoma randomized to surgery alone or to two 48-day cycles of infusional fluorouracil and cisplatin.[268] In contrast to all earlier studies reported, this trial performed modern presurgical staging including endoscopic ultrasound, CT scan, and laparoscopic staging, and only

۰۲۱-۶۶۱۹۸۵۱۴ www.myuptodate.com tahir99 - UnitedVRG دریافت آخرین نسخه آپتودیت آفلاین

endoscopic stage T3 to T4 tumors were eligible. The R0 resection was improved from 67% for surgery to 82% for preoperative chemotherapy ($p = 0.036$). At a median follow-up of 4.4 years, median survival was 65 months for the chemotherapy arm versus 63 months for surgery alone (HR, 0.84; $p = 0.466$) and 2-year overall survival was equivalent (70% for surgery alone, and 73% for the chemotherapy arm). Both arms had higher than expected median survival.

Despite the inconsistency of these outcomes, preoperative cisplatin and 5-FU is now the standard of care for resectable esophageal cancers—in particular, adenocarcinoma of the esophagus and GEJ—in the United Kingdom and in much of Europe, whereas this approach has not been generally accepted for esophageal cancer in the United States.

Preoperative Radiation Therapy. The high rate of local failure after esophagectomies engendered interest in the use of radiation therapy in conjunction with surgery. The incidence of local failure in the surgical control arms of randomized trials of preoperative radiation therapy reported by Mei et al.[271] and Gignoux et al.[272] was 12% and 67%, respectively. The local failure rate in the surgical control arm of the randomized trial of postoperative radiation therapy conducted by Teniere et al.[273] was 35% for patients with negative local–regional lymph nodes and 38% for patients with positive local–regional lymph nodes. The surgical control arm of INT-0113 provides a modern, more relevant baseline for the results of surgery alone. As discussed in Preoperative Chemotherapy, there was a 31% local failure rate in patients undergoing an R0 resection and a total local failure rate (including the additional 30% of patients with persistent disease) of 61%. Six randomized trials of preoperative radiation therapy for patients with clinically resectable disease have been reported.[263,271,272,274–276] Overall, preoperative radiation therapy did not increase the resectability rate, and only two series reported local failure rates. Although Mei et al.[271] reported no difference in local failure, Gignoux et al.[272] observed a significantly lower local failure rate in patients who received preoperative radiation therapy than in those treated with surgery alone (46% versus 67%, respectively).

Two trials have reported an improvement in survival. In the series of Nygaard et al.,[263] patients who received preoperative radiation therapy (with or without chemotherapy) had a significant improvement in overall 3-year survival (18% versus 5%; $p = 0.009$). The 48 patients who received preoperative radiation therapy without chemotherapy had a 20% 3-year survival rate; however, this did not reach statistical significance. This was not a pure radiation study, and the benefit may have been partly because of the chemotherapy. A similar improvement in survival was reported by Huang et al.[276] (46% versus 25%). A meta-analysis from the Oesophageal Cancer Collaborative Group also showed no clear evidence of a survival advantage with preoperative radiation therapy.[110]

Design flaws in these trials include the failure to use conventional doses of radiation therapy, the use of split-course radiation therapy, and failure to allow an adequate interval (4 to 8 weeks) between the completion of radiation therapy and surgery. The only study that allows an analysis of the effect of radiation fractionation is a randomized trial performed in France involving patients with squamous cell carcinomas who received chemoradiation using continuous-course versus split-course radiation.[277] The 95 patients who received a continuous-course regimen had a significantly higher local control rate (57% versus 29%) and 2-year event-free survival rate (33% versus 23%), and a borderline, significantly higher 2-year survival rate (37% versus 23%). Because it is less effective than continuous-course therapy, split-course radiation therapy is not recommended.

In summary, because only two of the six series have reported local failure rates, it is difficult to draw firm conclusions regarding the influence of preoperative radiation therapy on local control. Nonrandomized trials[278,279] also reported no survival benefit. Based on the available data from randomized trials, preoperative radiation therapy does not appear to significantly decrease local failure rate or improve survival in esophageal cancer patients.

Preoperative Chemoradiation. The rationale for trimodal therapy—chemoradiation followed by surgery—is based on the pattern of both local and distant failure associated with surgery alone or chemoradiation without surgery, which are the two treatment options established as standards of care based on data from randomized controlled trials. The results for patients randomly assigned to the surgery control arm of the INT-0113 trial revealed a 61% rate of failure in controlling local disease.[105] Similarly, the two Intergroup trials (RTOG-85-01 and INT-0123) that evaluated nonsurgical treatment (concurrent cisplatin and 5-FU, and radiotherapy), which are discussed in greater detail later in this chapter, showed unacceptably high rates of local failure (44% to 53%).[280,281] Most of the agents active against esophageal cancer (i.e., 5-FU, cisplatin, carboplatin, mitomycin C, paclitaxel, irinotecan, docetaxel, capecitabine, and oxaliplatin) are known to enhance radiosensitivity in cancer cells. Chemotherapy in conjunction with radiotherapy may both sensitize radiation therapy to improve local control as well as impact a reduction on systemic disease recurrence. Treatment with chemoradiation followed by an esophagectomy has the potential to: (1) downstage the disease, (2) increase the rate of complete resection with negative circumferential margins, and (3) eradicate occult micrometastatic disease.

Nonrandomized Trials. Most trials have used 5-FU and cisplatin-based chemotherapy combined with radiation therapy[111,282–301] although more recent trials incorporate paclitaxel, docetaxel, oxaliplatin, or irinotecan in two- or three-drug combination regimens.[101,302–314]

Since the initial trials by Leichman et al.[315] and the Southwest Oncology Group (SWOG-8037),[282] results of many phase II single-institution or multicenter trials of preoperative chemoradiation have been published.[316] Most trials used cisplatin (75 to 100 mg/m^2) and 5-FU (1,000 mg/m^2 per day continuous infusion for 4 or 5 days) with concurrent radiotherapy followed by surgery in 4 to 8 weeks. In most series, the pathologic complete-response rate (based on total number treated) was approximately 25%. The highest pathologic complete-response rates have been reported in trials treating mainly squamous cancers, and as more modern series predominantly treat adenocarcinoma, pathologic complete-response rates are consistently lower. Intensive chemoradiation regimens using hyperfractionated radiotherapy were evaluated by Forastiere et al.,[284,285] Raoul et al.,[295] and Adelstein et al.[292] Some of these regimens achieved higher pathologically determined complete-response rates and survival rates, usually with corresponding increases in acute toxicity. However, no clear advantage to altered fractionation schedules has been shown. The total dose of radiotherapy with concurrent chemotherapy varied from 30 Gy in earlier series up to 60 Gy, followed by surgery. Pathologic complete-response rates are uniformly in the 15% to 20% range with lower doses of radiation,[282,286,297,298] whereas total doses exceeding 50 Gy are associated with increased toxicity and perioperative complications.[296] Doses of 44 to 50 Gy using standard fractionation and concurrent therapy with cisplatin plus 5-FU generally result in pathologic complete-response rates of 25% to 40%[111,284,286,287,290,292,295,299] and acceptable toxicity with postoperative mortality rates well below 10%. As will be discussed later, the CROSS randomized trial of preoperative chemoradiation used 41.4 Gy and achieved a significant survival benefit with neoadjuvant therapy.[317]

Most trials use conventional fractionation and doses of radiotherapy (45.0 to 50.4 Gy) with concurrent chemotherapy. In addition to overall outcome, some investigators have sought to determine whether preoperative endoscopy with biopsy can accurately assess response to treatment and whether achievement of pathologically confirmed complete response after chemoradiation improves overall survival. Bates et al.[287] reported a 65% 3-year survival rate in patients who achieved a pathologic confirmed

۰۲۱-۶۶۱۹۸۵۱۴ www.myuptodate.com دریافت آخرین نسخه آپتودیت آفلاین

complete response, compared with a 25% survival rate in those who did not. In 106 of 262 (41%) patients who achieved a pathologic complete response with preoperative chemoradiation, the 5-year survival was 52% compared with 38% in partial responders ($p < 0.001$) and 19% in nonresponders ($p < 0.001$).[301]

In other trials with long-term follow-up, investigators observed 5-year survival rates of 60% to 67% and 27% to 32% for those with pathologic complete response and those with residual disease after induction therapy, respectively.[111,284] In addition, the fact that long-term survival was observed in approximately 30% of patients with a residual tumor in the resected specimen suggests that surgery is an important component following chemoradiation.

At present, no methods short of surgical resection can accurately determine which patients will be found to have no residual tumor in the resected esophageal specimen after chemoradiation. Bates et al.[287] noted a 41% false-negative rate with preoperative endoscopy and biopsy. Sarkaria et al.[318] reported the correlation of postchemoradiotherapy endoscopy findings and surgical pathologic findings in 156 patients with esophageal cancer. Although 76% had a biopsy-negative endoscopy after preoperative therapy, only 31% of these patients were found to be pathologic complete responders at subsequent surgery. Chedella et al.[319] reported the results of 284 patients who received preoperative chemoradiation at M.D. Anderson Cancer Center, and at 5 to 6 weeks posttreatment, underwent restaging with endoscopy, biopsy, and PET-CT scan. The 24% of patients who achieved a pathologic complete response (pCR) had a higher median survival compared to those who did not achieve a pCR (95 versus 55 months).[319] Of note, only 31% of patients who achieved a clinical complete response were found to have a pCR.

Yang et al.[320] made similar observations about the accuracy of posttherapy biopsy. Jones et al.[321] reported that CT scans had a sensitivity of 65%, a specificity of 33%, a positive predictive value of 58%, and a negative predictive value of 41% in evaluating pathologic response after preoperative chemoradiation in esophageal cancer patients. Many studies show that EUS performed after chemoradiation is also a poor predictor of complete response because of the inability to distinguish postirradiation fibrosis and inflammation from residual tumor. Reported staging accuracy is below 50%.[323–324]

To further pursue the selective surgical approach as a treatment modality, it will be critical to establish the definition of an adequate response. However, the ability to predict a pCR prior to surgery is variable. A multivariate analysis by Gaca and colleagues[325] reported that posttreatment nodal status ($p = 0.03$), but not the degree of primary tumor response, predicted disease-free survival. Fields et al.[326] reviewed 714 patients treated at Memorial Sloan Kettering Cancer Center (MSKCC) and reported that there was a significant improvement in 5-year survival in the 60 patients who achieved a pCR compared with the 549 who did not (55% versus 35%; $p = 0.036$).[326]

The value of FDG-PET scans for restaging after chemoradiation remains to be established. Several studies of esophageal cancer patients show that an early decrease in FDG uptake after chemotherapy can predict clinical response.[156,327,328] In addition, multiple studies have evaluated the ability of FDG-PET scans to predict a pCR following chemoradiation.[328–332] Flamen et al.[328] evaluated the predictive value of PET scans after chemoradiation in patients receiving preoperative treatment. The sensitivity and positive predictive value of PET scans for identifying a pathologically determined complete response were 67% and 50%, respectively. Both false-positive PET findings (residual FDG activity in an area of intense inflammatory activity on histopathologic analysis) and false-negative findings occurred at the primary tumor site. Vallbohmer et al.[329] treated 119 patients with preoperative chemoradiation (cisplatin, 5-FU, and 36 Gy) and reported a nonsignificant association between major responders and FDG-PET results ($p = 0.056$). However, there was no clear standardized uptake value threshold that predicted a response. Possible reasons for discrepant findings include the inflammatory effect of chemoradiation as well as a lack of standardization of FDG-PET protocols and techniques and definitions of a pathologic response.

Few studies have reported a long-term follow-up to determine actual survival rates at 5 years. Rates range from 25% reported by Bedenne et al.[297] for a series of 96 patients with squamous cell esophageal cancer to as high as 39% reported by Meredith et al.[301]

Taken together, data from nonrandomized trials accumulated during nearly 3 decades suggest an approximate 5% to 10% improvement in survival compared with historical surgery controls. However, substantially greater improvement in survival is seen in patients who are downstaged to pathologically confirmed complete response or minimal residual disease.

Patterns of failure after chemoradiation and resection are influenced by histologic type, with a greater likelihood of local recurrence for patients with squamous cell carcinoma of the esophagus and predominantly distant recurrence for those with adenocarcinoma of the distal esophagus, GEJ, and cardia. In a literature review of trials of preoperative chemoradiation published between 1980 and 2000, Geh et al.[316] found that the overall risk of relapse was 46%, but that the majority of relapses, 80%, were at distant sites; local–regional recurrence alone constituted only 9% of treatment failures. These cumulative data correspond with individual reports from other major centers[111,287,292,294] and suggest that preoperative chemoradiation followed by surgery leads to better local–regional control than does surgery alone or chemoradiation without surgery.

Newer regimens employing various combinations of 5-FU, cisplatin or oxaliplatin, taxanes, and irinotecan with radiotherapy report pathologic complete-response rates similar to those for previous cisplatin and 5-FU plus radiotherapy preoperative regimens, and rates of survival are also similar.

Meluch et al.[306] reported mature trial results for a combination of carboplatin, 5-FU, and paclitaxel plus concurrent radiotherapy. Among a total of 123 patients, the pathologic complete-response rate was 38%, and after a median follow-up of 45 months, the 3-year survival rate was 41%. Grade 3 or 4 leukopenia (73% of patients), esophagitis (43%), and hospitalization (57%) suggest that this regimen added toxicity without providing incremental improvement in survival. Toxicity on trials of paclitaxel and cisplatin on a once-weekly schedule, with conventional dose fractionation of radiation therapy, have reported lesser degrees of esophagitis.[303,308,333] McCurdy et al.[334] from the M.D. Anderson Cancer Center reported that the addition of taxanes to chemoradiation increased both the FDG-PET scan–determined pulmonary metabolic response and the radiation pneumonitis response compared with non–taxane-containing regimens. Weekly carboplatin combined with weekly paclitaxel and concurrent radiotherapy also appeared to have a favorable toxicity profile in a recent phase II trial treating 54 patients with adenocarcinoma and squamous cell carcinoma of the esophagus, and this regimen formed the basis of the recent Dutch CROSS Trial, which will be discussed.[310,317] The rate of pathologic complete response was 25%. Rates of grade 3 and 4 neutropenia (15%) and esophagitis (8%) were relatively low, but were in agreement with other trials employing a weekly paclitaxel and platinum drug chemotherapy regimen.

Swisher et al.,[308] Ajani et al.,[309] Bains et al.,[307] Ilson et al.,[101] and Rivera et al.[314] have published pilot experiences in the administration of induction chemotherapy before chemoradiotherapy and then surgery as a strategy to increase pathologically determined complete-response rate and to reduce distant failure. Some trials of induction chemotherapy have noted significant relief of patients' dysphagia and the rare need to place feeding tubes for nutritional support in patients.[101,307] The RTOG-0113 performed a phase II randomized trial comparing paclitaxel and 5-FU to paclitaxel and cisplatin plus radiation therapy.[312] Both arms were associated with significant toxicity, and the study did not meet its 1-year survival end point.

۰۲۱-۶۶۱۹۸۵۱۴ www.myuptodate.com tahir99 - UnitedVRG دریافت آخرین نسخه آپتودیت آفلاین

In summary, some of these newer regimens appear to be more toxic than cisplatin and 5-FU plus radiotherapy, whereas others suggest a potentially more favorable toxicity profile; the pathologic complete-response rates and survival estimates show no consistent benefit, but longer follow-up is needed. The interpretation of survival rates from these studies must be done cautiously, given the likelihood of stage migration due to the incorporation of EUS and PET scans into routine staging evaluation. Roof et al.[300] reported a single-institution experience of 177 patients treated with either cisplatin, 5-FU, or paclitaxel in combination with cisplatin, 5-FU, and radiation therapy as preoperative treatment in esophageal cancer. The 3-year overall survival was similar for the 5-FU/cisplatin–treated patients (39%) compared with those receiving paclitaxel in combination with 5-FU/cisplatin (42%). Pathologic complete-response rates were also comparable for two-drug (42%) compared with three-drug therapy (37%). In two sequential trials from Urba et al.[335,336] that evaluated two-drug paclitaxel cisplatin therapy plus radiation in one trial, and three-drug 5-FU, cisplatin, and paclitaxel plus radiation in another trial, there was also no difference in pathologic complete-response rates (17% to 19%). These rates of pathologic complete response were significantly lower than other trials reporting pathologic complete-response rates of 37% to 38% for three-drug therapy.[300]

The Eastern Cooperative Oncology Group (ECOG) reported response and survival[337] outcomes in a randomized phase II trial testing two of these combinations (E1201), limited to patients with resectable adenocarcinoma of the distal esophagus, GEJ, and cardia. The two preoperative treatments tested were (1) paclitaxel (50 mg/m^2, 1-hour infusion) followed by cisplatin (30 mg/m^2) on days 1, 8, 15, 22, 29, and concurrent radiotherapy (45 Gy); and (2) cisplatin (30 mg/m^2) followed by irinotecan (65 mg/m^2) on days 1, 8, 22, 29, and concurrent radiotherapy (45 Gy). Patients in each arm proceeded to esophagectomy followed by three cycles of adjuvant paclitaxel and cisplatin (arm 1) or cisplatin and irinotecan (arm 2). Staging with esophageal EUS was an eligibility requirement. A preliminary report indicated comparable rates of pathologic complete response for the two regimens of 15% to 16%, with the lower than expected pathologic complete-response rate likely partly due to the exclusive treatment of adenocarcinoma on this trial.[338] The median survival on the paclitaxel arm was 20.9 months, and 34.9 months on the irinotecan arm (difference nonsignificant). Although the results are comparable to other modern phase II trials in esophageal adenocarcinoma, neither regimen appeared superior to more conventional 5-FU and cisplatin-based therapy.

Randomized Trials. Randomized trials comparing preoperative chemoradiation with surgery alone in patients with clinically resectable disease are listed in Table 45.7.[107,114,240,317,339–344] The series of Le Prise et al.[345] is not included because patients received sequential rather than concurrent chemotherapy and radiotherapy. Most trials combined cisplatin and 5-FU[339–341] or single-agent cisplatin[240] with concurrent radiotherapy.

The Bosset et al.[240] trial was limited to patients with stage I or II squamous cell carcinoma based on a previously defined CT scan staging system, whereas the trials of Urba et al.,[107] Burmeister et al.,[341] Tepper et al.,[342] and van Hagen et al.[317] treated adenocarcinoma and squamous cell carcinoma, and the trial of Walsh et al.[339,340] was designed for locally advanced, resectable adenocarcinoma. A significant difference in the median and 3-year survival rates was observed in the Walsh, Tepper, and Van Hagen et al. trials. It is noteworthy that the pathologically determined complete-response rate was consistent for all studies, 25% to 28%, with the exception of the Burmeister et al. trial, which indicated a statistically significant lower pathologic complete-response rate for adenocarcinoma (9%) compared to squamous cell carcinoma (27%). Van Hagen et al. reported a pathologic complete response rate of 24% for adenocarcinoma and 49% for squamous cell carcinoma. Comparable rates of 3-year survival for patients in each of the investigational treatment groups (30% to 40%) was also observed. Higher 5-year survival rates, however, were reported on the Tepper et al. trial (39%) and the Van Hagen et al. trial (47%).

Urba et al.[107] at the University of Michigan randomly assigned 100 patients (75 with adenocarcinoma, 25 with squamous cell

TABLE 45.7

Results of Preoperative Chemoradiation for Esophageal Cancer: Randomized Trials

Study (Ref.)	No. of Patients (n)	Histology	Chemotherapy	RT (Gy)	R0 Resection (%)	Pathologic Complete Response (%)	Median Survival (months)	Overall Survival 3-, and 5-Year Overall Survival (%)
Bosset et al.[240]	282	S	C + RT + surgery Surgery	37	78 68	26	19 19	5 yr: 26 5 yr: 26
Walsh et al.[339]	113	A	CF + RT + surgery	40	NS NS	25 —	16 11	3 yr: 32 3 yr: 6
Urba et al.[107]	100	S/A	CF + RT + surgery Surgery	45	90 90	28 —	18 17	3 yr: 30 3 yr: 16
Burmeister et al.[341]	256	S/A	CF + RT + Surgery Surgery	35 44	80 59	9 (A) 27 (S) —	22 19	NS NS
Tepper et al.[342]	56	S/A	CF + RT + surgery Surgery	50.4	NS NS	40 —	54 22	5 yr: 39 5 yr: 16
Van Hagen et al.[317]	366	S/A	CaP + RT + surgery Surgery	41.4	92 69	24 (A) 49 (S) —	49 24	3 yr: 58 5 yr: 47 3 yr: 50 5 yr: 34
Lee et al.[343]	102	S	CF + RT + surgery Surgery		NS NS	49 —	28 27	3 yr: 46 3 yr: 46

S, squamous cell carcinoma; C, cisplatin; RT, radiation therapy; A, adenocarcinoma; NS, not stated; Ca, carboplatin; P, paclitaxel.

۰۲۱-۶۶۱۹۸۵۱۴ www.myuptodate.com دریافت آخرین نسخه آپتودیت آفلاین

carcinoma) to receive (1) preoperative cisplatin (20 mg/m^2 on days 1 to 5 and 17 to 21), vinblastine (1 mg/m^2 on days 1 to 4 and 17 to 20), 5-FU (300 mg/m^2 per 24 hours on days 1 to 21), and concurrent radiotherapy (1.5 Gy twice a day to 45 Gy), followed on day 42 by a transhiatal esophagectomy, or (2) immediate surgery. A survival analysis after a median follow-up of 8.2 years for surviving patients revealed a nonsignificant improvement favoring preoperative chemoradiation (3-year survival, 30% versus 16%; $p = 0.15$). A significant decrease in local–regional recurrence as a component of first failure was observed (19% recurrence rate for the combined treatment group versus 42% for the group undergoing immediate surgery; $p = 0.02$). However, there was no difference in the rates of distant metastases, 60% and 65%, respectively. Although overall survival rates were not significantly different, there was a 31% lower risk of death, after adjustment for other prognostic factors, for patients randomly assigned to receive trimodal therapy, which suggests a possible benefit and the need for a trial adequately powered to detect a smaller survival difference. Consistent with phase II trial data, patients who achieved a pathologically confirmed complete response had better survival outcomes, with a median survival time of 50 months and 3-year survival rate of 64%, compared to those with residual disease in the resected specimen, who had a median survival time of 12 months and a 3-year survival rate of 19%. The low statistical power of this trial may have failed to detect a potential modest survival benefit for chemoradiation compared to surgery alone.

In their series, Walsh et al.[339] reported a significant survival advantage for patients receiving preoperative chemoradiation. A total of 113 patients with adenocarcinoma of the esophagus, GEJ, and cardia were randomly assigned to receive (1) two cycles (weeks 1 and 6) of 5-FU (15 mg/kg per 24 hours on days 1 to 5), cisplatin (75 mg/m^2 on day 7), plus concurrent radiotherapy (2.67 Gy per day to 40 Gy) followed by esophagectomy; or (2) immediate surgery alone. Chemoradiation was well tolerated. The incidence of acute toxicity of grade 3 or higher was 15%. The operative mortality was 9% in the multimodality treatment arm compared with 4% in the surgery control arm. After a median follow-up of surviving patients of 18 months, a significant improvement in both median survival time (16 months versus 11 months; $p = 0.01$) and 3-year survival rate (32% versus 6%; $p = 0.01$) was observed in patients who received preoperative therapy compared with those treated with surgery alone. A major criticism of this trial was the low 3-year survival rate (6%) in the surgical control arm. This probably reflects a patient population with more advanced disease than in those enrolled in the other two trials. CT scan staging was not required. More than 80% of patients had lymph node metastases.[340]

A third randomized trial of preoperative chemoradiation was reported by Bosset et al.[240] of the EORTC. A total of 282 patients with clinically resectable (early stage I and II) squamous cell carcinoma were randomly assigned to undergo either preoperative chemoradiation or surgery alone. The preoperative regimen consisted of five daily fractions of 3.7 Gy each followed by a 2-week rest and another 3.7 Gy for 5 days. Chemotherapy was limited to cisplatin, 80 mg/m^2, 0 to 2 days before starting each 5 days of radiotherapy. Rates of curative resection were significantly higher in patients undergoing preoperative chemoradiation (81%) compared with immediate surgery (69%). After a median follow-up of 55 months, patients who received preoperative chemoradiation had a significantly better 3-year disease-free survival rate (40% versus 28%) and local disease-free survival (relative risk [RR], 0.6), yet had no improvement in median survival time (19 months) or overall 3-year survival (36%) compared with patients treated with surgery alone. However, this chemoradiation regimen was unconventional in design; not only was the radiation split course and delivered with unusually high doses per fraction, but the doses of chemotherapy would not be considered adequate for systemic therapy. The threefold higher postoperative mortality in the combined modality arm (12%) compared with the surgery-alone arm (4%) may have undercut any potential overall survival benefit for chemoradiation.

The trial reported by Burmeister et al.[341] treated 256 patients with adenocarcinoma and squamous cell carcinoma with either surgery alone, or preoperative cisplatin, 5-FU, and radiation followed by surgery. The combined modality arm received one cycle of 5-FU dosed at 800 mg/m^2 per day during a 4-day continuous infusion in combination with cisplatin 80 mg/m^2 on day 1, plus concurrent radiotherapy (2.33 Gy per day to 35 Gy) followed by esophagectomy. Chemoradiation was well tolerated, with the most common toxicities grade 3 or 4 esophagitis (16%) or nausea and vomiting (5%). There was no difference in surgical complications in either treatment group, with an overall operative mortality of 5%. After a median follow-up of 65 months, no significant difference was seen in either median overall survival time (22 months versus 19 months with surgery alone) or 3-year survival rate. The chemoradiation group had a higher rate or curative resection (80%) compared with the surgery-alone arm (59%). Pathologic complete responses were significantly less common in adenocarcinoma (9%) compared with squamous cell carcinoma (27%). A univariate analysis indicated that patients with squamous cell cancer had significantly better progression-free and overall survival when treated with preoperative chemoradiation. The low rate of pathologic complete responses in patients with adenocarcinoma on this trial raises concern about the adequacy of chemotherapy delivered (one cycle) during radiotherapy.

A similar trial was reported by Lee et al.[343] from Korea. A total of 102 patients with squamous cell cancer were randomized to surgery alone versus preoperative therapy with 45.6 Gy (1.2 Gy twice a day) plus 5-FU/cisplatin. There was no difference in median survival (28 months versus 27 months).

The sixth randomized trial by Tepper et al.[342] reported the results of an Intergroup trial led by the Cancer and Leukemia Group B (CALGB-9781), in which patients were randomly assigned to receive either (1) immediate surgery or (2) two cycles of cisplatin, 5-FU, and concurrent radiotherapy (total dose, 50.4 Gy) followed by surgery. This trial, activated in July 1998 and projected to enroll 475 patients, was terminated early because of failure to meet accrual targets. However, follow-up was available in 56 patients ultimately randomized and treated on protocol. With a median follow-up of 6 years, 5-year survival was significantly improved with the addition of preoperative chemoradiation (39% versus 16%; $p = 0.005$). Interpretation of this trial is confounded by the small number of patients treated.

The most contemporary trial recently reported by Van Hagen et al., the CROSS Trial,[317] has for many practitioners established a new standard or care for preoperative chemoradiotherapy. This study randomized 366 patients with squamous cell carcinoma or adenocarcinoma of the esophagus or GEJ to treatment with (1) preoperative carboplatin at an area under the curve of 2 mg/mL per minute and paclitaxel 50 mg/m^2 once weekly for 5 weeks, and concurrent radiotherapy (1.8 Gy daily to 41.4 Gy in 23 fractions, followed by transthoracic esophagectomy or transhiatal esophagectomy for GEJ cancers, or (2) immediate surgery. Unlike earlier trials, this more modern trial staged all patients by endoscopic ultrasound and CT scan, and patients were required to have either node-positive or T2-3Nany disease. The majority of patients treated had adenocarcinoma (75%), and most tumors involved the distal third of the esophagus (58%). The majority of patients were node positive (65%), and slightly more patients on the chemoradiotherapy arm had T3 tumors (84%) compared to the surgery-alone arm (78%). At a median follow-up of 45 months, the trial showed a significant survival benefit (Fig 45.13) for chemoradiotherapy added to surgery, with a median survival increased from 24 to 49 months (HR, 0.0657; $p = 0.003$), and improvement in 2- and 5-year overall survival (67% and 47% versus 50% and 34%; HR, 0.665). The rate of R0 resection was significantly improved on the chemoradiotherapy arm (95% compared

۰۲۱-۶۶۱۹۸۵۱۴ www.myuptodate.com tahir99 - UnitedVRG دریافت آخرین نسخه آپتودیت آفلاین

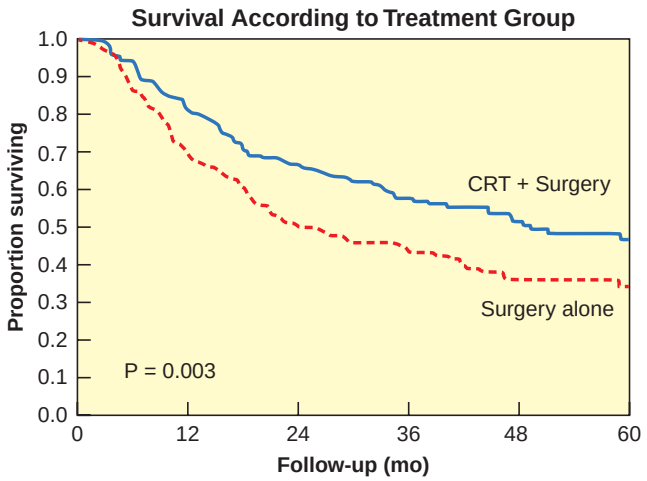

Figure 45.13 Overall survival CROSS trial comparing patients randomized to preoperative chemoradiotherapy (CRT + surgery) versus surgery alone.

to 69%; p <0.001). Pathologic complete responses were seen in 24% of adenocarcinomas and 49% of squamous cancers. Survival benefits were significant for both histologies, but with an even greater benefit for squamous cancers (HR, 0.453) compared to adenocarcinomas (HR, 0.741). Therapy was well tolerated with grade 3 or 4 hematologic toxicity seen in 7% patients, and grade 3 or 4 nonhematologic toxicity seen in less than 13%. There was no difference in either operative morbidity or mortality, and mortality was below 4% in each arm, which is considered consistent and appropriate with modern day surgical outcomes in high-volume centers. Many investigators feel that this well-conducted chemoradiotherapy trial using a well-tolerated, relatively easy to administer therapeutic regimen established a new standard of care for squamous cell carcinomas and adenocarcinomas of the distal esophagus or GEJ.

Some additional insight may be obtained from a small trial reported by Stahl et al.,[344] a multicenter phase III trial directly comparing preoperative chemotherapy to combined chemoradiotherapy followed by surgery in patients with GEJ adenocarcinoma. The trial did not meet accrual goals and randomized only 119 eligible patients with Siewert I to III GEJ adenocarcinoma. The strength of the trial was the rigorous pretherapy staging, including EUS and laparoscopy, and the balance in treatment arms by clinical stage. Patients were assigned to (1) 2.5 cycles of a 6-week schedule of weekly 5-FU 2 g/m^2, 24-hour infusion and leucovorin 500 mg/m^2, 2-hour infusion plus biweekly cisplatin 50 mg/m^2, or (2) two cycles of the same regimen, followed by 3 weeks of radiotherapy given in 15 fractions at a dose of 2 Gy combined with cisplatin 50 mg/m^2 on day 1 and 8 and etoposide 80 mg/m^2 on days 3 to 5. The primary end point was 3-year overall survival. Comparable numbers of patients had an R0 resection after chemotherapy (69.5%) compared to chemoradiotherapy (72%). More patients on the chemoradiotherapy arm achieved a pathologic complete response (15.6%) compared to the chemotherapy arm (2.0%), and more patients were node negative (64.4% compared to 36.7%, respectively). Three-year survival trended superior in the chemoradiotherapy group (47.4%) compared to the chemotherapy group (27.7%; p = 0.07), and freedom from local tumor progression also favored the chemoradiotherapy group (76.5% versus 59%; p = 0.06). More in-hospital deaths occurred in the chemoradiotherapy arm (10.2% versus 3.8%; not statistically significant). The authors concluded that preoperative chemoradiotherapy could be considered a standard of care based on the favorable comparison to preoperative chemotherapy alone.

The accumulated experience from phase II and III trials indicates the following concerning chemoradiation using cisplatin and infusional 5-FU–based therapy followed by an esophagectomy:

- In approximately two-thirds of patients, the disease is downstaged.
- A survival advantage exists for patients experiencing downstaging to pathologically confirmed complete response or minimal residual disease status.
- Surgery appears to be an important component of treatment to eliminate persistent disease after chemoradiation, especially for adenocarcinoma. Of this group, 20% to 30% will be long-term survivors. The higher rates of pathologic complete response for squamous cancers make an argument for primary chemoradiotherapy without surgery, and this issue will be reviewed in the Radiation Therapy section.
- Local–regional control is improved, whereas distant failure is frequent and is the major cause of death.
- Rates of curative resection may be improved with preoperative chemoradiation.

Controversy continues about the optimal management of adenocarcinoma of the distal esophagus or GEJ, in particular the relative merits of preoperative chemotherapy versus combined chemoradiotherapy followed by surgery. Two ongoing randomized trials may shed light on this debate once completed. One trial, the CRITICS trial being run in the Netherlands and Sweden (NCT00407186), assigns patients with adenocarcinoma of the distal esophagus, GEJ, and stomach to all receive pre- and postoperative chemotherapy in addition to surgery; patients are randomized postoperatively to continue to receive either chemotherapy alone, or to chemotherapy combined with postoperative radiotherapy. Another trial, TOPGEAR (NCT01924819), being run by the Australasian Gasto-Intestinal Trials Group (AGITG) will treat patients with esophageal, GEJ, or gastric cancers with perioperative chemotherapy, with patients randomized to receive combined radiation therapy with preoperative chemotherapy or to preoperative chemotherapy alone.

Meta-analyses lend support to the inclusion of chemotherapy and radiation therapy as part of surgical management. Two studies evaluated in a combined analysis randomized trials predominantly of preoperative chemotherapy[346] and preoperative chemotherapy and radiation therapy compared to surgery alone.[347] These studies pooled the results of 11 to 25 randomized trials treating between 2,300 and nearly 4,200 patients. Preoperative chemotherapy improved 2-year survival by 5.1% to 6.3% for preoperative chemotherapy alone, and preoperative combined chemoradiation improved 2-year survival by 8.7%. Because of the toxicity and ongoing controversy about the benefit associated with preoperative combined chemoradiation, the priority should be given to enrolling patients in clinical trials.

Targeted Agents

Limited studies have evaluated the combination of a targeted agent with either definitive, nonoperative chemoradiotherapy, or preoperative chemoradiotherapy. Two pilot trials combining the vascular endothelial growth factor (VEGF) ligand-targeted agent, bevacizumab, added to chemoradiotherapy failed to improve outcome compared to historical controls.[313,348] The EGFR-targeted agent cetuximab was combined with definitive chemoradiotherapy in two recently reported trials. First is the SCOPE-1 trial where 258 patients with stages I through III cancer (25% adenocarcinoma) were randomized to 50 Gy/capecitabine/cisplatin ± cetuximab without planned surgery.[349] The trial was stopped early since it met its futility rules. Patient who received cetuximab had inferior 2-year survival (41% versus 56%) and higher nonheme grade 3+ acute toxicity (79% versus 63%). The second is the recently completed RTOG 0436 trial in which patients with nonoperable esophageal cancer were randomized to 50.4

۰۲۱-۶۶۱۹۸۵۱۴ www.myuptodate.com دریافت آخرین نسخه آپتودیت آفلاین

Gy/paclitaxel ± cetuximab, reported only in abstract form.[350] On this nonoperative trial, of the 328 patients, the majority had adenocarcinoma. There was no difference in outcome with the addition of cetuximab to chemoradiotherapy, with no increase in rates on endoscopic clinical complete response, and no differences in overall survival and no impact on either adenocarcinoma of squamous cell carcinoma histology. These negative results add to the accumulating literature, also discussed in the section on metastatic disease, that currently available EGFR-targeted therapies are ineffective in esophageal cancer. A phase I/II trial combining the HER2-targeted agent trastuzumab with chemoradiotherapy[351] in esophageal cancer led to a randomized phase III trial in esophageal adenocarcinoma being conducted by RTOG (NCT01196390). Patients with esophageal or GEJ adenocarcinoma whose tumors test HER2 positive are randomized to chemoradiotherapy with weekly carboplatin AUCS 2 and paclitaxel 50 mg/m^2 for six doses combined with 50.4 Gy of radiotherapy followed by surgery, with or without the addition of trastuzumab during chemoradiotherapy and as a surgical adjuvant therapy for 1 year after surgery. As will be reviewed in the section covering advanced disease, with the exception of trastuzumab, suitable targets as well as active targeted agents remain to be established in the combined modality treatment of esophageal cancer.

Postoperative Chemotherapy. Administering chemotherapy after surgery to patients who have already received chemotherapy or chemoradiation preoperatively has not been easily achieved in phase II[257,258,299] and phase III trials.[105,264] This is exemplified by the INT-0113 trial, in which only 38% of patients who were candidates for adjuvant cisplatin and 5-FU therapy received the two planned courses.[105]

In Japan, surgery includes the removal of the primary lesion plus extended dissection of lymph nodes in the mediastinum, neck, and abdomen. The Japanese Oncology Group has evaluated postoperative chemotherapy in a series of randomized trials.[352–355] One study of 205 patients who had undergone resection compared observation with two courses of adjuvant cisplatin and vindesine.[354] Median follow-up was 59 months, and the 5-year survival rate was 45% in the control arm and 48% in the adjuvant treatment arm, which indicated no survival benefit from this chemotherapy regimen.

A second trial of adjuvant chemotherapy in 242 patients had the same study design, except that the chemotherapy was cisplatin and 5-FU administered for two courses after curative resection.[353,355] At a median follow-up of 40.4 months, no differences were observed in the 5-year survival estimates (51% versus 61% for adjuvant chemotherapy; $p = 0.3$). The estimated 5-year disease-free survival rate was improved with chemotherapy (58% for the chemotherapy versus 46% for observation; $p = 0.05$). Disease-free survival for node-negative patients was 77% in the surgery-alone group versus 82% in the adjuvant treatment group ($p = 0.3$), and for node-positive patients 35% in the surgery-alone group versus 53% in the adjuvant treatment group ($p = 0.06$). These data suggest that adjuvant chemotherapy may benefit node-positive patients, but this was an unplanned subset analysis on this trial. The ECOG completed a phase II trial (E8296) to evaluate adjuvant therapy consisting of cisplatin (75 mg/m^2) and paclitaxel (175 mg/m^2 during 3 hours) every 3 weeks for four courses in 55 patients with completely resected, T3, or node-positive adenocarcinoma of the esophagus, GEJ, or cardia.[356] The majority (89%) had lymph node involvement. The majority of these (84%) were able to complete all four cycles of chemotherapy. The 2-year survival rate was 60%, which compared favorably with results for contemporary historical controls.[105]

In summary, the available data for postoperative adjuvant chemotherapy suggest a possible prolongation of survival for patients who have had a potentially curative (R0) resection and have lymph node–positive (N1) disease. There are no data to indicate or suggest that the administration of postoperative adjuvant chemotherapy will prolong survival for patients who have undergone a curative resection and have negative nodes (N0). Patients who have positive margins of resection should be considered for postoperative radiation. Those who have had R0 resections but have regional nodal metastases (stages IIB and III) should be enrolled in clinical trials to evaluate adjuvant therapies.

Postoperative Radiation Therapy. Several reports of nonrandomized trials have suggested that postoperative radiation therapy may be effective after esophagectomy. Yamamoto et al.[357] reported a 94% 2-year local control rate in node-positive patients. For patients who underwent a three-field dissection, Hosokawa et al.[358] added intraoperative radiation followed by 45 Gy postoperatively. The 5-year survival rate was 34%.

Two randomized trials were limited to patients treated in the adjuvant setting. Teniere et al.[273] reported the results for 221 patients with squamous cell carcinoma randomly assigned to receive either surgery alone or postoperative radiation therapy (45 to 55 Gy at 1.8 Gy per fraction). Postoperative radiation therapy was found to have no significant impact on survival. In the series of Fok et al.,[359] patients with both squamous cell carcinomas and adenocarcinomas receiving either curative or palliative resections were evaluated; although the total dose of radiation therapy was conventional, the dose per fraction (3.5 Gy) was unconventional. No significant decrease in local failure or distant failure or improvement in the median survival time was achieved with the addition of postoperative radiation therapy.

Postoperative Chemoradiation. The only randomized trial of postoperative chemoradiation is the Intergroup trial INT-0116.[360] Although the goal of this trial was to examine the role of postoperative adjuvant chemoradiation in gastric cancer, 20% of patients had adenocarcinoma of the GEJ. Eligible patients included those with stage IB, II, IIIA, IIIB, or IV nonmetastatic adenocarcinoma of the stomach or GEJ after curative resection. Patients were randomly assigned to receive either observation alone or postoperative chemoradiation consisting of four monthly cycles of bolus 5-FU and leucovorin plus 45 Gy concurrent radiation with cycle two. A total of 603 patients were registered. Pretreatment characteristics were similar in both arms, and most patients had locally advanced disease. Approximately two-thirds of the patients had pT3 or pT4 tumors and approximately 85% had positive local–regional nodes.

Patients randomly assigned to receive postoperative chemoradiation had a significant decrease in local failure as the first site of failure (19% versus 29%) and an increase in median survival (36 months versus 27 months), 3-year relapse-free survival (48% versus 31%), and overall survival (50% versus 41%; $p = 0.005$). Although 17% of patients could not complete all therapy as planned, there was only one treatment-related death. With a median follow-up of 10 years, the improvement in survival with postoperative chemoradiation remains statistically significant.[360] An analysis of the impact of HER2 status in the INT-0116 trial revealed that HER2-negative patients had a survival benefit from chemoradiation whereas patients who underwent surgery only did not.[361]

The other role for postoperative radiation therapy is in cases of positive surgical margins. Based on the RTOG-85-01 trial, patients selected for treatment with postoperative radiation should receive chemoradiation.[280,362,363]

Definitive Chemoradiation

Although definitive chemoradiation is a treatment option for patients with localized resectable esophageal carcinoma, especially those with cervical esophageal squamous cell carcinoma or those not considered ideal resection candidates, this therapeutic approach is discussed in detail in Chemoradiation in the next section.

۰۲۱-۶۶۱۹۸۵۱۴ www.myuptodate.com tahir99 - UnitedVRG دریافت آخرین نسخه آپتودیت آفلاین

Treatment of Locally Advanced Disease

Radiation Therapy

The 1996 to 1999 patterns of care study examined 414 patients who received radiation therapy as part of definitive or adjuvant management at 59 institutions.[364] Overall, 51% had adenocarcinoma and 49% had squamous cell carcinoma. With a median follow-up of 8 months, a multivariate analysis revealed that patients who received chemoradiation followed by surgery had a significant decrease in local–regional recurrence (HR, 0.40; $p < 0.0001$) and survival (HR, 0.32; $p = 0.001$) compared with those who did not undergo surgery. A similar significant decrease in local–regional recurrence (HR, 1.36; $p = 0.01$) and survival (HR, 1.32; $p < 0.03$) was seen in those patients who received their care at large radiation oncology centers (treating 500 or more new cancer patients per year) compared with small centers (treating fewer than 500 new cancer patients per year). In a similar patterns of care study of 767 patients treated in Japan from 1998 to 2001, 220 (29%) received preoperative or postoperative radiation, or both, with or without chemotherapy.[365]

The effect of histologic type (adenocarcinoma versus squamous cell carcinoma) is unclear. Most series suggest that squamous cell cancers have a higher response rate compared with adenocarcinomas; however, no clear difference in outcome was found. The National Cancer Institute Intergroup has randomized trials that stratify patients by lesion histologic type. Until these data are available, the impact of histologic type cannot be adequately assessed, and it is reasonable to treat both types of lesions in a similar fashion.

Primary Nonsurgical Therapy. Primary therapy for esophageal cancer is either surgical or nonsurgical. The patient population selected for treatment with each modality is usually different. For several reasons, this results in a selection bias against nonsurgical therapy. Patients with unfavorable prognostic features are more commonly selected for treatment with nonsurgical therapy. These features include medical contraindications and primary unresectable or actual metastatic disease. Surgical series report results based on pathologic stage, whereas nonsurgical series report results based on clinical stage. Pathologic staging has the advantage of excluding some patients with metastatic disease not identified during clinical staging. Because some patients treated without surgery are approached in a palliative rather than a curative fashion, the intensity of chemotherapy and the doses and techniques of radiation therapy used may be suboptimal.

The difficulty of accurately staging esophageal cancer preoperatively is discussed in Diagnostic Studies and Pretreatment Staging, earlier in this chapter. The efficacy of FDG-PET scans as a complement to CT scans and EUS must be emphasized. Undetected metastatic disease was identified by PET scans in 15% of patients in the series by Flamen et al.[328] and in 20% of patients in the series by Downey et al.[327]

Radiation Therapy Alone. Many series have reported results of external-beam radiation therapy alone. Most include patients with unfavorable features such as clinical T4 disease and multiple positive lymph nodes. For example, in the series of De-Ren,[366] 184 of the 678 patients had stage IV disease. Overall, the 5-year survival rate for patients treated with conventional doses of radiation therapy alone is 0% to 10%.[362,366,367] The use of radiation therapy as a potentially curative modality requires doses of at least 50 Gy at 1.8 to 2.0 Gy per fraction. Shi et al.[368] reported a 33% 5-year survival rate with the use of late-course accelerated fractionation to a total dose of 68.4 Gy. However, in the radiation-therapy–alone arm of the RTOG-85-01 trial in which patients received 64 Gy at 2 Gy per day with modern techniques, all patients were dead of their disease by 3 years.[280,363]

Collectively, these data indicate that radiation therapy alone should be reserved for palliation or for patients who are medically unable to receive chemotherapy. As is discussed in the following section, the results of chemoradiation are more favorable, and it remains the standard of care.

Definitive Chemoradiation

Conventional Approaches

Comparison of Definitive Chemoradiation and Surgery. There are many single-arm, nonrandomized trials of chemoradiation alone, and they have included patients with disease at a variety of stages.[335–338] Few series examine patients with T1 or T2 disease.[369,370] In the series reported by Coia et al.,[369] patients received 5-FU and mitomycin C concurrently with 60 Gy of radiation therapy. When results for clinical stage I and II disease are combined, the local failure rate was 25%, the 5-year actuarial local relapse-free survival was 70%, and the 5-year actuarial survival was 30%.

Six randomized trials compared radiation therapy alone with chemoradiation.[114,263,280,371–375] Of these six trials, five used suboptimal doses of radiation and three used inadequate doses of systemic chemotherapy, and some studies used sequential chemotherapy and radiotherapy rather than concurrent therapy. For example, in the series of Araujo et al.,[375] patients received only one cycle of 5-FU, mitomycin C, and bleomycin. The EORTC trial used subcutaneous methotrexate.[371] In the Scandinavian trial reported by Nygaard et al.,[263] patients received low doses of chemotherapy (cisplatin, 20 mg/m^2, and bleomycin, 10 mg/m^2, for a maximum of two cycles). An analysis of pooled data from these trials reported a significant local control and survival benefit at 1 year for chemoradiation compared with radiation therapy alone.[376] Chemoradiation was associated with a significant increase in adverse effects, including life-threatening toxicities.

In the ECOG EST-1282 trial,[374] patients who received chemoradiation had a significantly increased median survival compared with those who received radiation alone (15 months versus 9 months; $p = 0.04$) but experienced no improvement in 5-year survival (9% versus 7%). However, this was not a pure nonsurgical trial because approximately 50% of patients in each arm underwent surgery after receiving 40 Gy of radiation. Furthermore, this decision depended on the individual investigator's preference. The operative mortality was 17%. Finally, the Pretoria trial reported by Slabber et al.,[373] which was limited to a total of 70 patients with T3 squamous cell cancers, used a low-dose (40 Gy) split-course radiation schedule.

The only trial that was designed to deliver adequate doses of systemic chemotherapy with concurrent radiation therapy was the RTOG-85-01 trial reported by Herskovic et al.,[280] and updated by Al-Sarraf et al.[372] This Intergroup trial primarily included patients with squamous cell carcinoma. Patients received four cycles of 5-FU (1,000 mg/m^2 per 24 hour × 4 days) and cisplatin (75 mg/m^2 on day 1). Radiation therapy (50 Gy at 2 Gy per day) was given concurrently with day 1 of chemotherapy. Curiously, cycles three and four of chemotherapy were delivered every 3 weeks (weeks 8 and 11) rather than every 4 weeks (weeks 9 and 13). This intensification may explain, in part, why only 50% of the patients finished all four cycles of the chemotherapy. The control arm was given radiation therapy alone, albeit at a higher dose (64 Gy) than the chemoradiation arm.

Patients who received chemoradiation had a significant improvement in median survival (14 months versus 9 months) and 5-year survival (27% versus 0%; $p < 0.0001$).[344] There was a clear plateau in the survival curve. Minimum follow-up was 5 years, and the 8-year survival was 22%.[114,375] The histologic type did not significantly influence the results: 21% of patients with squamous cell carcinomas (n = 107) were alive at 5 years compared with 13% of patients with adenocarcinoma (n = 23) (p was not significant). Although African Americans had larger primary tumors, all of which were squamous cell cancers, there was no difference in their survival compared with that of Caucasians.[377] The incidence of local

۰۲۱-۶۶۱۹۸۵۱۴ www.myuptodate.com دریافت آخرین نسخه آپتودیت آفلاین

failure as the first site of failure (defined as local persistence or recurrence) was also decreased in the chemoradiation arm (47% versus 65%). The protocol was closed early because of the positive results; however, after this early closure, an additional 69 eligible patients were treated with the same chemoradiation regimen. In this nonrandomized combined modality group, the 5-year survival was 14% and local failure was 52%.

Chemoradiation not only improves the results compared with radiation alone but also is associated with a higher incidence of toxicity. In the 1997 report of the RTOG-85-01 trial, patients who received chemoradiation had a higher incidence of acute grade 3 toxicity (44% versus 25%) and acute grade 4 toxicity (20% versus 3%) compared with those who received radiation therapy alone. Including the one treatment-related death (2%), the incidence of total acute grade 3+ toxicity was 66%.[372] The 1999 report examined late toxicity. The incidence of late grade 3+ toxicity was similar in the chemoradiation arm and in the radiation-alone arm (29% versus 23%).[114] However, grade 4+ toxicity remained higher in the combined modality arm (10% versus 2%). Interestingly, the nonrandomized chemoradiation group experienced a similar incidence of late grade 3+ toxicity (28%) but a lower incidence of grade 4 toxicity (4%), and there were no treatment-related deaths.

Based on the positive results from the RTOG-85-01 trial, the conventional nonsurgical treatment for esophageal carcinoma is chemoradiation. Notwithstanding, the local failure rate in the RTOG-85-01 chemoradiation arm was 45%, and there is room for improvement. Therefore, new approaches, such as intensification of chemoradiation and escalation of the radiation dose, have been developed in an attempt to help improve these results.

Randomized Trials. Although there are a number of trials comparing preoperative chemoradiation with surgery alone, there are only two trials that directly compare nonoperative treatment with surgery. One randomized trial compared surgery with radiation alone[378] and one compared surgery with chemoradiation.[379] Both series have small numbers of patients, limited follow-up, and neither report a difference in survival.

Nonrandomized Trials. The positive results of RTOG-85-01, demonstrating a 27% 5-year survival rate for patients treated with definitive chemoradiation compared with no 5-year survival after treatment with radiotherapy alone, is a major advance. This treatment option has influenced the selection of patients for nonsurgical management because it provides an alternative for restoring swallowing function in patients with locally advanced disease for whom resection would likely be palliative.

For patients with earlier-stage disease that appears resectable, definitive chemoradiation may also be appropriate treatment; however, prospective trials comparing this approach with surgery, stratified by stage, have not been performed. Nonetheless, nonrandomized comparisons of contemporary series suggest that the nonsurgical approach offers a survival rate that is the same or better than that achievable with surgery alone. For example, the median survival time and 5-year survival rate were 14 months and 27%, respectively, in the chemoradiation arm of RTOG-85-01, and 20 months and 20%, respectively, in INT-0122.[380] In comparison, the median survival in the surgical control arm of the Dutch trial reported by Kok et al.[269] was 11 months, and the median survival time and 5-year survival rate in the surgical control arm of INT-0113 were 16 months and 20%, respectively. Likewise, the local failure rates were similar. The incidence of local failure (local recurrence plus local persistence of disease) as the first site of failure was 45% in RTOG-85-01 and 39% in INT-0122. If all patients, including patients failing to undergo surgery or patients having an R2 resection are included, the local failure as the first site of failure was 61% on the surgical trial INT-0113, which is actually higher than the 45% reported on RTOG-85-01. The treatment-related mortality rates were also similar (2% in RTOG-85-01, 9% in INT-0122, and 6% in INT-0113).

In summary, the local failure, survival, and treatment-related mortality rates for nonsurgical and surgical therapies are similar. Although the results are comparable, it is clear that both the nonsurgical and surgical approaches have limited success.

Necessity for Surgery After Chemoradiation. Two randomized trials examine whether surgery is necessary after chemoradiation. In the Fédération Francaise de Cancérologie Digestive (FFCD) 9102 trial, 444 patients with clinically resectable T3-4N0-1M0 squamous cell or adenocarcinoma of the esophagus received initial chemoradiation.[116] Patients initially received two cycles of 5-FU, cisplatin, and concurrent radiation (either 46 Gy at 2 Gy per day or split course 15 Gy weeks 1 and 3). The 259 patients who had at least a partial response were then randomized to surgery versus additional chemoradiation, which included three cycles of 5-FU, cisplatin, and concurrent radiation (either 20 Gy at 2 Gy per day or split course 15 Gy). Two-year local control was 66% in the surgery arm versus 57% in the chemoradiation-alone arm. There was no significant difference in 2-year survival (34% versus 40%; $p = 0.44$) or median survival (17.7 months versus 19.3 months) in patients who underwent surgery versus additional chemoradiation. These data suggest that patients who initially respond to chemoradiation should complete chemoradiation rather than stop and undergo surgery. Using the Spitzer index, there was no difference in global quality of life; however, a significantly greater decrease in quality of life was observed in the surgery arm during the postoperative period (7.52 versus 8.45; $p < 0.01$, respectively).[381] A separate analysis revealed that compared with split course radiation, patients who received standard course radiation had improved 2-year local relapse-free survival rates (77% versus 57%; $p = 0.002$) but no significant difference in overall survival (37% versus 31%).[382]

The German Oesophageal Cancer Study Group compared preoperative chemoradiation followed by surgery versus chemoradiation alone.[117] In this trial, 172 eligible patients age 70 years or more with uT3-4N0-1M0 squamous cell cancers of the esophagus were randomized to preoperative therapy (three cycles of 5-FU, leucovorin, etoposide, and cisplatin, followed by concurrent etoposide, cisplatin, plus 40 Gy) followed by surgery versus chemoradiation alone (the same chemotherapy but the radiation dose was increased to 60 to 65 Gy with or without brachytherapy). The pathologic complete response (pCR) rate was 33%. Despite a decrease in 2-year local failure (36% versus 58%; $p = 0.003$), there was no significant difference in 3-year survival (31% versus 24%) for those who were randomized to preoperative chemoradiation followed by surgery versus chemoradiation alone.

The current standard of care is to perform esophagectomy following chemoradiation in patients that can tolerate this approach. However, it is known that a subset of patients will have a complete response to chemoradiation. Further, patients with pCR have improved survival. Data from both Berger et al.[383] and Rohatgi et al.[384] suggest that patients who achieve a pCR had an improvement in survival compared to those who do not (5-year: 48% versus 15%, and median: 133 months versus 34 months, respectively). In these patients, surgical resection may not be necessary and has led to the concept of *selective* surgery after preoperative chemoradiation.

Swisher et al.[385] reported a retrospective analysis of patients who underwent a salvage compared with a planned esophagectomy at the M.D. Anderson Cancer Center from 1987 to 2000. The operative mortality was higher in those who underwent salvage versus planned surgery (15% versus 6%), but there was no difference in survival (25%). Because only 13 patients were identified who had salvage, the results need to be interpreted with caution. This approach formed the basis of a phase II Radiation Therapy Oncology Group (RTOG) trial (RTOG 0246), which prospectively examined the approach of preoperative paclitaxel/CDDP and 50.4 Gy followed by selective surgery in patients with either residual disease or recurrent disease in the absence of distant metastasis. In this trial of 43 patients with locally advanced disease, 21 patients required surgical resection after chemoradiation due to residual

۰۲۱-۶۶۱۹۸۵۱۴ www.myuptodate.com tahir99 - UnitedVRG دریافت آخرین نسخه آپتودیت آفلاین

(17 patients) or recurrent (3 patients) disease and one patient by choice.[386] This approach led to a 1-year overall survival of 71% and was closed early because it did not meet the predetermined survival rate of 78%.

Tumor Markers and Predictors of Response to Chemoradiation. It would be helpful to predict which tumors have a higher likelihood of responding to radiation or chemoradiation. Geh et al.[316] performed a systematic review to identify factors associated with a higher rate of pCR in patients receiving preoperative chemoradiation. The analysis was limited to the 26 trials meeting four criteria: (1) at least 20 patients treated, (2) a single chemoradiation regimen was delivered, (3) 5-FU, cisplatin, or mitomycin C–based chemotherapy was used, and (4) there was information on patient numbers, age, resection, and pCR rates. Overall, the pCR rate was 24% and the probability of pCR increased with increasing radiation dose ($p = 0.006$) and the use of a 5-FU-based ($p = 0.003$) or cisplatin-based ($p = 0.018$) regimen. In contrast, increased radiation treatment time ($p = 0.035$) and median age ($p = 0.019$) both decreased the chance of a pCR.

Data from both Berger et al.[383] and Rohatgi et al.[384] suggest that patients who achieve a pCR had an improvement in survival compared with those who do not (5-year, 48% versus 15%, and median, 133 months versus 34 months, respectively). However, the ability to predict a pCR prior to surgery is variable, as discussed earlier. A multivariate analysis by Gaca et al.[387] reported that posttreatment nodal status ($p = 0.03$), but not the degree of primary tumor response, predicted disease-free survival. Studies have linked tumor lymphocytic infiltration as well as the apoptotic index with response to chemoradiation.[388] Additional studies have linked a large number of proteins and genes involved in a wide array of signaling cascades with response to chemoradiation. Examples include alterations in diverse signaling cascades involving PI3 kinase, p53, EGFR, and hypoxia-inducible factor 1 alpha (HIF-1a).[389–394] Unfortunately, the vast majority of these studies lack validation and the specificity required to be used clinically. One recent study generated a micro-RNA signature to predict pCR from tumors in 52 patients treated uniformly with chemoradiation.[395] This signature was then validated in a separate cohort of 72 patients treated similarly. When combined with clinical stage, the area under the curve (AUC) for pathologic complete response (pCR) was 0.77 ($p = 2 \times 10^{-41}$).

Posttreatment imaging does not consistently identify the response. An ultrasound following chemoradiation does not accurately predict a pCR.[396] In contrast, Blackstock et al.[397] reported that the percentage of decrease in standard uptake value measured by 18F-FDG-PET predicted response, and Brucher et al.[398] found that it correlated with survival. McLoughlin et al.[399] treated 81 patients with preoperative chemoradiation and reported that FDG-PET scans were able to predict a pathologic complete response with 62% sensitivity, 44% specificity, and 56% accuracy.

The predictive ability of molecular markers has been examined. In 38 patients with squamous cell carcinoma who received chemoradiation with or without surgery, tumors without *p53* expression and tumors with weak *Bcl-X_L* expression showed a higher response to chemotherapy (56% and 53%, respectively) than tumors positive for *p53* or with strong *Bcl-X_L* expression (30% and 32%, respectively; *p* not significant).[400] After preoperative chemoradiation, patients with *p53*-negative tumors had a significantly better mean survival than those with *p53*-positive tumors (31 months versus 11 months; $p = 0.0378$). By multivariate analysis, Pomp et al.[401] found that overexpression of p53 resulted in a decrease in the survival in 69 patients with squamous cell carcinoma or adenocarcinoma treated with radiation alone. In one study, there was a correlation between decreasing levels of four phospholipids and increasing T stage and grade.[402]

Understanding the mechanism of radioresistance through the identification and targeting of molecular pathways by serum protein profiling[403] and the identification of genes involved in apoptosis,[404] activated transcription factor nuclear factor κB (NF-κB),[392] and microvascular density[405] may offer new opportunities for therapeutic advances.

Intensification of Chemoradiation. The phase II Intergroup trial 0122 (ECOG-PE289/RTOG-90-12) was designed to intensify treatment in the RTOG-85-01 combined modality arm.[381] Both the chemotherapy and radiation therapy in INT-0122 were intensified by 20%.[406] The median survival time was 20 months and the 5-year actuarial survival rate was 20%. Similar toxicities were reported by Ishikura et al.[407] for 139 patients with squamous cell cancers treated with 5-FU, cisplatin, and 60 Gy of radiation. However, the higher radiation dose (64.8 Gy) in INT-0122 was tolerated and compared with the 50.4 Gy of radiation in the Intergroup trial INT-0123, discussed as follows.

A potential advantage of neoadjuvant chemotherapy is the early identification of those patients who may or may not respond to the chemotherapeutic regimen being delivered concurrently with chemoradiation. Ilson et al.[101] have shown that the change in standard update value (SUV) on FDG-PET scan was able to predict which patients showed a response to the full course of chemotherapy followed by chemoradiotherapy. Weider and associates[408] reported similar findings in 38 patients with squamous cell cancers. As discussed previously, the use of an early PET scan during induction chemotherapy to direct subsequent chemotherapy during combined chemoradiotherapy is the subject of an ongoing Alliance Trial.

Amini et al.[409] performed a retrospective review of 141 patients who achieved an initial clinical complete response (cCR) after chemoradiation. By a multivariate analysis, the initial SUV of >10 and poorly differentiated tumors had a significantly higher incidence of in-field failure.[409]

Intensification of the Radiation Dose. Another approach to the dose intensification of chemoradiation is increasing the radiation dose above 50.4 Gy. There are two methods by which to increase the radiation dose to the esophagus: brachytherapy and external-beam radiation therapy.

Brachytherapy. Intraluminal brachytherapy allows for the escalation of the dose to the primary tumor while protecting the surrounding dose-limiting structures such as the lung, heart, and spinal cord.[410] A radioactive source is placed intraluminally via bronchoscopy or a nasogastric tube. Brachytherapy has been used both as primary therapy (usually palliative)[411,412] and as a boost after external-beam radiation therapy or chemoradiation.[413–415] It can be delivered by high-dose rate or low-dose rate.[416] Although there are technical and radiobiologic differences between the two dose rates, there are no clear therapeutic advantages for either.

Series that combine brachytherapy with external-beam radiation therapy or chemoradiation report results similar to those for conventional chemoradiation. Yorozu et al.[415] reported a local failure rate of 57% and a 5-year actuarial survival of 28% in 46 patients with stage T2-3N0-1M0 disease. Even for a more favorable subset of patients with clinical T1 to T2 disease, Yorozu et al.[417] reported a local failure rate of 44% and a 5-year survival of 26%. In the series by Pasquier et al.,[414] local failure was 23% and 5-year survival was 36%. In an updated series by Ishikawa et al.,[418] 59 patients with submucosal esophageal cancer received external-beam therapy followed by brachytherapy in 36 patients with either low-dose rate caesium-137 (^{137}Cs) (17 patients) or high-dose rate iridium-192 (^{192}Ir) (19 patients). Patients selected to receive a brachytherapy boost had a significantly higher 5-year cause specific survival (86% versus 62%; $p = 0.04$).

In the RTOG-92-07 trial, 75 patients with squamous cell cancers (92%) or adenocarcinomas (8%) of the thoracic esophagus received the RTOG-85-01 combined modality regimen (5-FU, cisplatin, and 50 Gy of radiation) followed by a boost during cycle three of chemotherapy with either low-dose rate or high-dose rate intraluminal brachytherapy.[419] Because of low accrual, the low-dose rate option was discontinued and the analysis was limited

۰۲۱-۶۶۱۹۸۵۱۴ www.myuptodate.com دریافت آخرین نسخه آپتودیت آفلاین

to patients who received the high-dose rate treatment. High-dose rate brachytherapy was delivered in weekly fractions of 5 Gy during weeks 8, 9, and 10. After the development of several fistulas, the fraction delivered at week 10 was discontinued. Although the complete-response rate was 73%, the rate of local failure was 27%. Rates of acute toxicity were 58% for grade 3, 26% for grade 4, and 8% for grade 5 (treatment-related death). The cumulative incidence of fistula was 18% per year and the crude incidence was 14%. Of the six treatment-related fistulas, three were fatal. Given the significant toxicity, this treatment approach should be used with caution.[420] Based on these and other data, the American Brachytherapy Society has developed guidelines for esophageal brachytherapy.[421–423]

External-Beam Therapy: 2D and 3D Techniques. Because almost all patients in both the INT-0122 trial who started radiation therapy were able to complete the full dose (64.8 Gy), this higher dose of radiation was used in the experimental arm of the Intergroup esophageal trial INT-0123 (RTOG-94-05).[281] In this trial, patients with either squamous cell carcinoma or adenocarcinoma who were selected for nonsurgical treatment were randomly assigned to receive a slightly modified RTOG-85-01 combined modality regimen with 50.4 Gy of radiation versus the same chemotherapy with 64.8 Gy of radiation.

The modifications to the original RTOG-85-01 chemoradiation arm includes (1) using 1.8-Gy fractions to 50.4 Gy rather than 2-Gy fractions to 50 Gy; (2) treating with 5-cm proximal and distal margins for 50.4 Gy rather than treating the whole esophagus for the first 30 Gy followed by a cone down with 5-cm margins to 50 Gy; (3) cycle three of 5-FU and cisplatin did not begin until 4 weeks after the completion of radiation therapy rather than 3 weeks after; and (4) cycles three and four of chemotherapy were delivered every 4 weeks rather than every 3 weeks.

INT-0123 was closed to accrual in 1999 with 218 patients after an interim analysis revealed that it was unlikely that the high-dose arm would achieve superior survival compared with the standard-dose arm: There was no significant difference in median survival time (13.0 months versus 18.1 months) or 2-year survival rate (31% versus 40%) between the high-dose and standard-dose arms.[281] Although 11 treatment-related deaths occurred in the high-dose arm compared with 2 in the standard-dose arm, 7 of the 11 deaths occurred in patients who had received 50.4 Gy or less.

Although the crude incidence of local failure or persistence of local disease (or both) was lower in the high-dose arm than in the standard-dose arm (50% versus 55%), as was the incidence of distant failure (9% versus 16%), these were not significant. Although retrospective data from the M.D. Anderson Cancer Center suggest a positive correlation between radiation dose and local–regional control,[422] the results of the INT-0123 trial maintain the standard dose of 50.4 Gy.

The modifications to the original RTOG-85-01 chemoradiation arm outlined earlier did not adversely affect the local control or survival rate in the control arm of INT-0123. Therefore, the radiation doses and field design used in the control arm of INT-0123 should be used.

Radiation can be intensified not only by increasing the total dose, but also by using accelerated fractionation or hyperfractionation. This approach has revealed modest results. Zaho and colleagues[424] treated 201 patients with squamous cell cancer using 41.4 Gy followed by late-course accelerated hyperfractionation to 68.4 Gy. The results were similar to RTOG 85-01 (38% local failure and 26% 5-year survival). Choi and colleagues[425] treated 46 patients with 5-FU/cisplatin and twice per day radiation using a concurrent boost technique and reported a 37% 5-year survival. Additionally, Lee et al.[343] reported on a trial of 102 patients with locally advanced disease, limited to squamous cell carcinoma, randomized to surgery alone versus preoperative therapy with 45.6 Gy (1.2 Gy twice per day) plus 5-FU/cisplatin. There was no difference in median survival (28 versus 27 months). Thus, although these approaches appear to be reasonable, there appears to be a significant increase in acute toxicity without any clear therapeutic benefit.

Dose Escalation: Intensity Modulated Radiation Therapy and Protons. A criticism of many dose escalation trials in the definitive management of locally advanced esophageal cancer is the use of conventional two-dimensional (2D) and three-dimensional (3D) radiation techniques. Trials using newer techniques such as intensity-modulated radiation therapy (IMRT) and protons may be able to deliver higher doses of radiation with a more tolerable toxicity profile. Multiple dosimetric studies comparing standard 3D-conformal radiotherapy and IMRT, generally have found improved sparing of the heart, lung, or both using either static field or arc-based IMRT.[426–435] This has led multiple clinical centers to begin the routine use of IMRT in this disease. A retrospective analysis of these data does not suggest an inferior outcome and may provide decreased toxicity versus non-IMRT treatment techniques.[436–438] Investigators at the M.D. Anderson Cancer Center reported the results of 676 patients with locally advanced disease treated with either IMRT (263 patients) or 3D conformal radiation therapy (3DCRT) (413 patients).[436] On a multivariate analysis, IMRT was associated with improved survival ($p = 0.004$), but not cancer-specific survival ($p = 0.86$). The survival difference between 3DCRT and IMRT was thought to be due to a higher level of cardiac deaths ($p = 0.05$) and unexplained deaths ($p = 0.003$) in the 3DCRT patients, suggesting that decreased cardiac dose may have a direct impact on patient outcome. Although this and other comparisons between 3DCRT and IMRT are retrospective, a randomized trial is unlikely, thus the available data may represent the best comparison.

Another theoretical advantage of IMRT is the possibility of dose escalation. With the use of IMRT, a simultaneous integrated boost (SIB) may be performed while maintaining commonly used lung and heart dosimetric constraints. Retrospective data from Zhang and colleagues[422] suggest a positive correlation between radiation dose and local–regional control. This has led to a phase I studying examining this approach in locally advanced disease. However, at this point, based on results of the INT-0123 trial, the standard dose of external beam radiation remains 50.4 Gy.

New Chemoradiation Regimens. Because 75% to 80% of patients die of metastatic disease, advances in systemic therapies are necessary for a further improvement of results. The most widely used chemotherapeutic regimen to be combined with radiation for the treatment of esophageal cancer is 5-FU and cisplatin. A number of new cytotoxic and targeted regimens are being evaluated in both the preoperative and nonoperative setting. These are discussed previously in the section on preoperative chemoradiation regimens.

Palliation of Esophageal Cancer with Radiation Therapy

Palliation of Dysphagia and Bleeding. Many of the series examining dysphagia are retrospective, and most do not use objective criteria to define and assess dysphagia. Some do not report the number of patients presenting with dysphagia or the percentage who receive palliative treatment until the time of death. Furthermore, few series carefully examine other variables that may influence the results, such as histologic type, stage, and location of the primary tumor.

Options for palliation include stents, feeding tubes, chemotherapy, and external-beam radiation therapy or brachytherapy (or both). The selection of the technique is variable and commonly is based on physician preference. In a randomized trial from the Dutch SIREC Study Group of stent versus one 12-Gy fraction of brachytherapy, dysphagia, as measured by a variety of quality-of-life scales, improved more rapidly after stent placement; however, long-term relief was

۰۲۱-۶۶۱۹۸۵۱۴ www.myuptodate.com tahir99 - UnitedVRG دریافت آخرین نسخه آپتودیت آفلاین

superior after brachytherapy.[412] Median survivals were similar (145 days versus 155 days).

Patients for whom stents fail are commonly treated with palliative radiation. Li et al.[439] reported that the presence of a metal stent increases the radiation dose 5% to 10% at a 0.5-cm depth in the esophageal wall. Therefore, the radiation dose should be decreased by 5% to 10% when a metal stent is in the radiation field. Nishimura et al.[440] reported a high-grade 3+ complication rate in 47 patients who underwent stent placement before or during radiation treatment and recommend that stent placement be delayed until radiation therapy has failed.

As seen in Table 45.8, series have examined the palliative benefits of either radiation alone[371,441–444] or chemoradiation.[406,443,445–450] Overall, external-beam radiation therapy alone provides palliation of dysphagia in 70% to 80% of patients.

The most comprehensive and carefully performed analysis of swallowing function in patients receiving chemoradiation is by Coia et al.[450] Using a swallowing score modified from O'Rourke et al.,[451] they analyzed 102 patients treated with three 5-FU–based combined modality regimens. Before the start of therapy, 95% of patients had some degree of dysphagia. Within 2 weeks after the start of treatment, 45% had improvement in dysphagia, and by the completion of the 6-week therapy, 83% had improvement. Overall, 88% experienced an improvement in dysphagia. The median time to improvement was 4 weeks (range, 1 to 21 weeks), and all but two patients could swallow at least soft or solid foods. Harvey et al.[446] treated 106 patients and reported that 78% had improvement of at least one grade in their dysphagia score; 51% maintained swallowing improvement until the time of last follow-up.

Intraluminal brachytherapy is also an effective, albeit a more limited method, achieving palliation of dysphagia in 35% to 80% of patients and a median survival of 5 months. A major limitation of brachytherapy is the effective treatment distance. The primary isotope is ^{192}-Ir, which is usually prescribed to treat to a distance of 1 cm from the source. Any portion of the tumor that is more than 1 cm from the source will receive a suboptimal radiation dose, confirmed by pathologic analysis of surgical specimens.[452] Given its limited effective range, brachytherapy is usually not as successful as external-beam radiation therapy in treating the entire tumor volume. However, in a randomized trial, there was no difference in local control or survival with high-dose–rate brachytherapy as opposed to external-beam radiation therapy.[452]

If a patient requires rapid palliation (within a few days), alternative approaches such as laser treatment or stent placement are recommended. Although external-beam radiation with or without chemotherapy takes at least 2 weeks to produce palliation, once palliation is achieved it is more durable than that provided by the other palliative modalities because external-beam radiation treats the problem (the gross tumor mass), not just the symptom. If external-beam radiation is not possible, then intraluminal brachytherapy should be considered because it is an effective modality for decreasing symptoms such as dysphagia and bleeding. Chemotherapy by itself may also substantially relieve dysphagia when used as an initial treatment of metastatic disease.

Treatment in the Setting of Tracheoesophageal Fistula

The presence of a malignant tracheoesophageal fistula usually results in poor survival, although occasionally, patients may survive for a prolonged period. Historically, radiation therapy was believed to be contraindicated for these patients for fear of exacerbating the fistula as the tumor responded. More recently, there have been reports to the contrary. In a Mayo Clinic series, 10 patients with malignant tracheoesophageal fistulas received 30 to 66 Gy external-beam radiation, and the median survival time was 5 months.[453] A series from Japan that treated 24 patients with fistulization to the airway reported ultimate closure of the fistula after chemoradiotherapy in 17 patients, with time to closure ranging from 6 to 280 days.[454]

TABLE 45.8

Palliation of Dysphagia with Radiation Therapy with or without Chemotherapy

Study (Ref.)	No. of Patients	Palliation of Dysphagia[a]	
		At the End of Treatment (%)	Duration
Raditation Therapy Alone			
Wara et al.[441]	103	89	6-mo average
Petrovich et al.[442]	133	87	34% = 6 mo 18% = 3 mo 35% = 3 mo
Roussel et al.[371]	69	70	—
Caspers et al.[444]	127	71	54% until death
Whittington et al.[443]	25	—	5% at 9 mo
Chemoradiation			
Coia et al.[450]	102	88	67%–100% until death
Seitz et al.[445]	35	100[b]	—
Whittington et al.[443]	26	—	87% 3-y actuarial
Algan et al.[447]	8	100	—
Gill et al.[448]	71	60	—
Urba et al.[449]	27	—	59% until death
Izquierdo et al.[406]	25	64	Median, 5 mo
Harvey et al.[446]	106	78	51% until lost follow-up

[a] See text for definition and number of patients presenting with dysphagia.
[b] Patients had dilation or neodymium yttrium-aluminum garnet laser treatment at the start of therapy.

۰۲۱-۶۶۱۹۸۵۱۴ www.myuptodate.com دریافت آخرین نسخه آپتودیت آفلاین

Although the experience is very limited, the data suggest that radiation treatment does not necessarily increase the severity of a malignant tracheoesophageal fistula and it can be administered safely. It is unclear if radiation treatment improves outcome.

Acute and Long-Term Toxicity of Radiation Therapy. The toxicity of radiation therapy is a function of what the total dose is, what technique is used, and whether the patient has received chemotherapy. Essentially all patients experience lethargy and esophagitis commencing 2 to 3 weeks after the start of radiation therapy; these symptoms usually resolve 1 to 2 weeks after completion of therapy.

The most carefully documented acute toxicity data for patients who receive radiation therapy alone (without chemotherapy) are from the control arm of RTOG-85-01 in which patients received radiation therapy alone to a dose of 64 Gy.[280,372] The incidence of acute grade 3 toxicity was 25% and the incidence of acute grade 4 toxicity was 3%. The incidence of long-term grade 3+ toxicity and long-term grade 4+ toxicity was 23% and 2%, respectively. Radiation therapy can produce esophageal strictures, as can surgery. The total incidence of stricture (benign plus malignant) in patients receiving radiation therapy alone or radiation combined with chemotherapy is 20% to 40% in a modern series and up to 60% in historical series,[455] with up to 50% malignant, associated with recurrence. The incidence of stricture is lower in series in which careful radiation techniques were used. Coia et al.[450] examined a subset of 25 patients who experienced local control and survived at least 1 year. The incidence of benign stricture was 12%. Radiation toxicity is related to dose–volume effects.[456]

One series examined the functional outcomes of benign and malignant strictures.[451] Patients received 45 to 56 Gy and 53% received some form of chemotherapy. Of the 24 patients (30%) who developed a benign stricture, 71% were able to tolerate a full or soft diet and required dilation, with a median interval between dilations of 5 months. Even in the subset of patients who develop a benign stricture, dilation is effective in the majority of patients. In contrast, in the 28% of patients who developed a malignant stricture, dilation was unsuccessful and esophageal intubation was required.

The high incidence of fistula reported in the RTOG-92-07 trial of chemoradiation plus intraluminal brachytherapy (18% actuarial, 14% crude) has not been seen in series using radiation therapy or chemoradiation. The incidence of other long-term grade 3+ toxicities such as pneumonitis or pericarditis is 5%.

The effect of radiation on pulmonary function was examined by Gergel et al.[457] Patients received 39.6 Gy with anterior–posterior fields followed by radiation with oblique fields to a total dose of 50.4 Gy, plus concurrent chemotherapy with oxaliplatin and 5-FU. Results of pulmonary function tests administered before and a median of 16 days after radiation revealed significant declines in diffusing capacity for carbon monoxide and total lung capacity. Investigators at the M.D. Anderson Cancer Center performed retrospective treatment-planning studies on 10 patients and found that IMRT reduced the dose volume of exposed normal lung but had no clinically meaningful differences on the irradiated volumes of spinal cord, heart, liver, or total body integral doses.[426] The impact of respiratory and organ movement on defining target volumes is being investigated.[458,459]

The issue of treatment-related deaths in patients who receive chemoradiation is complex. Although the incidence was only 2% in RTOG-85-01, subsequent trials have reported a higher treatment-related mortality rate (i.e., 9% in INT-0122 and 8% in RTOG-92-07). These mortality rates are lower than the 10% to 15% incidence reported in historical surgical series, although only slightly higher than the 6% reported in the surgical control arm of INT-0113.[105] It is interesting to note that, as the mortality rate with surgery has decreased, there has been a corresponding increase in the treatment-related mortality rate reported in the nonoperative trials. As previously discussed in Primary Nonsurgical Therapy, this may be partly related to bias in selecting patients to be treated with the nonoperative approach.

Radiation Field Design and Treatment Techniques. Just as expert surgical skills are required for a successful esophagectomy, radiation field design for esophageal cancer requires careful planning. Historically, the standard radiation dose, based on INT-0123, for patients selected for chemoradiation is 50.4 Gy at 1.8 Gy per fraction. However, recent data from the CROSS trial suggest that 41.4 Gy in the same fractionation may be sufficient to treat in the preoperative setting. As previously described, some investigators have performed dose escalation; however, based on INT-0113, dose escalation above 50.4 Gy should not be performed off protocol. Additionally, radiation should be delivered without treatment breaks, as randomized data from France reveal a higher local control (57% versus 29%) and 2-year survival rate (37% versus 23%) with continuous course compared with split course radiation.[382]

The radiation field should include the primary tumor with 5 cm superior and inferior margins and 2 cm lateral margins. The primary local–regional lymph nodes should receive the same dose. For cervical (proximal) primary tumors (defined as at or proximal to the carina), the treatment volume includes the bilateral supraclavicular nodes, and for GEJ (distal) primaries, the celiac axis nodes should be included.

Treatment Modality. At many centers, the standard of care in radiotherapy for locally advanced esophageal cancer is 3D conformal radiotherapy using a beam arrangement optimized via CT scan–based planning. However, as mentioned previously, many clinicians have used IMRT with a possible benefit with regard to toxicity and no apparent compromise in oncologic outcome.[436] A comparison of three techniques is shown in Figure 45.14. If IMRT is to be used, careful attention should be given to target delineation. In addition, particularly in the case of distal/GEJ tumors, 4D CT or other forms of motion management should be considered.

Recently, proton radiotherapy has become more available as a treatment modality. By virtue of its physical characteristics, proton radiotherapy is thought to decrease dose to critical structures, in large part by minimizing the low-dose "bath" often seen with IMRT. This is to some degree shown in dosimetric studies, with V5, V10, and V20 to the lung and heart with protons compared to IMRT (see Fig. 45.14). Several studies have examined patient outcome after treating with proton radiotherapy. Sugahara and colleagues[460] examined outcomes in 46 patients with squamous cell carcinoma treated with protons with or without photons to a median total dose of 76 Gy.[460] The 5-year local control rate was for T1: 83%, for T2 through 4: 29%, and for survival T1: 55% and for T2 through 4: 13%. Koyama[461] reported mean actuarial survival rates of 60% for patients with superficial and 39% for those with advanced disease treated to mean total doses of 78 to 81 Gy. The incidence of esophageal ulcer was 67%. In the United States, Lin and colleagues[462] retrospectively reviewed 62 patients treated with proton radiotherapy for locally advanced disease. Overall, 47% were treated with surgical resection following chemoradiation, with a pCR rate in these patients of 28%. In this series, two patients (3.2%) developed symptomatic pneumonitis and an additional two patients died due to treatment-related factors. Proton therapy remains experimental and is currently being evaluated in a randomized trial.

Target Delineation. Although CT scans can identify adjacent organs and structures, it may be limited in defining the extent of the primary tumor. Leong and colleagues[463] have demonstrated that the addition of PET/CT scan information for treatment planning improved the identification of the gross tumor volume (GTV). The GTV based on CT scan information alone excluded PET-avid disease in 11 of 16 patients (69%), 5 of whom would have resulted in a geographic miss of gross tumor. Thus, in many centers, it is

۰۲۱-۶۶۱۹۸۵۱۴ www.myuptodate.com tahir99 - UnitedVRG دریافت آخرین نسخه آپتودیت آفلاین

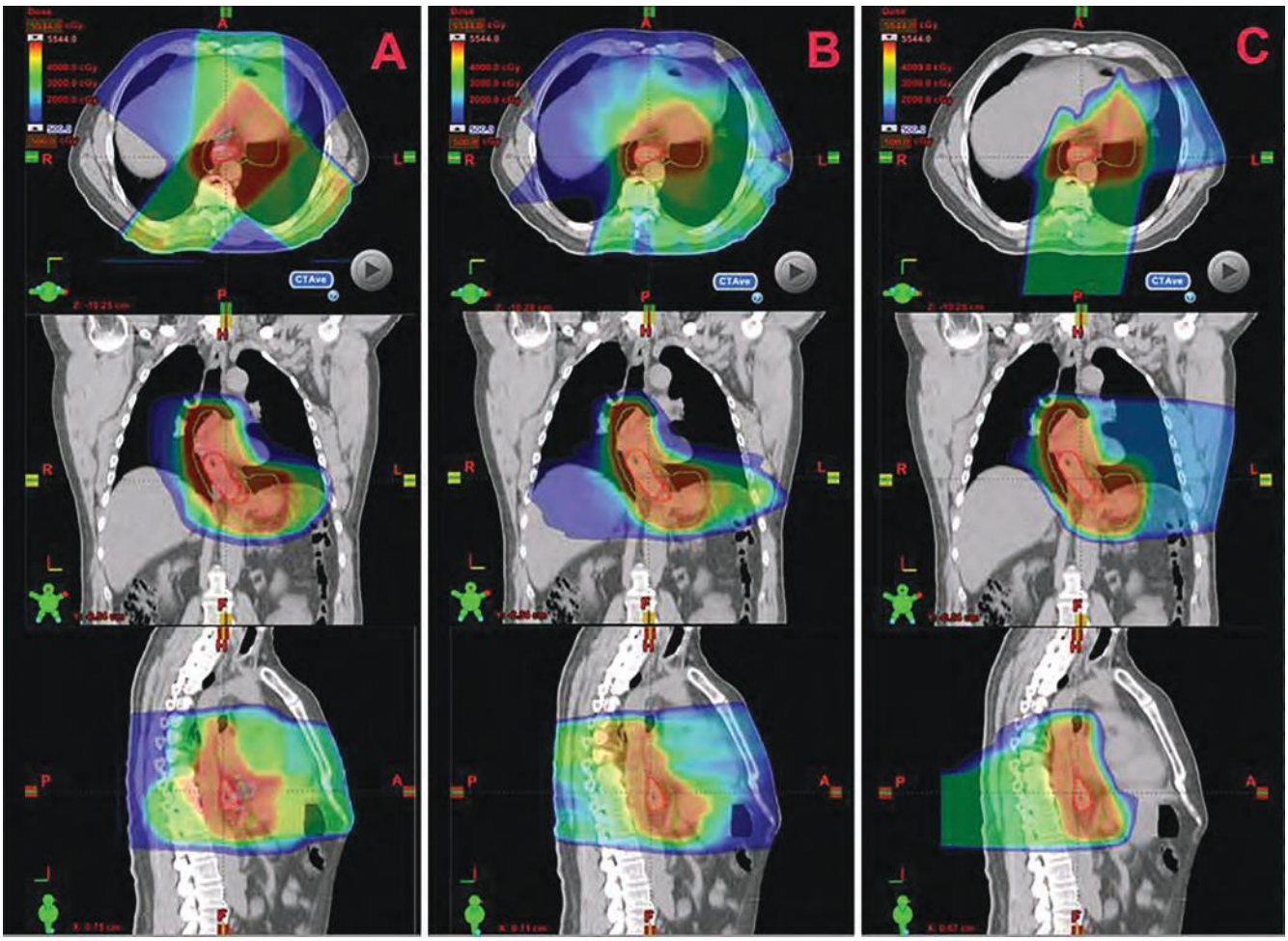

Figure 45.14 Comparative radiation treatment plans. **(A)** 3D-CRT, **(B)** IMRT, and **(C)** proton beam comparison between treatment modalities. In this selected case, both IMRT and protons provide improved lung and cardiac sparing compared to 3D-CRT. Proton beam decreases liver dose compared to other modalities. (Modified from Zhang Z, Liao Z, Jin J, et al. Dose response relationship in locoregional control for patients with stage II–III esophageal cancer treated with concurrent chemotherapy and radiotherapy. *Int J Radiat Oncol Biol Phys* 2005;61:656–664.)

customary to obtain pretreatment FDG-PET scans, not only to identify patients with occult metastatic disease, but also to assist in target delineation. Conversely, MRI has also been suggested to delineate esophageal tumors, although initial studies showed limited benefit in tumor or positive lymph node delineation.[464] Thus, the use of MRI in this context remains experimental. Thus, the current recommendation for target delineation includes using contrasted CT and EGD/EUS findings, as well as FDG-PET.

Limiting Toxicity of Chemoradiation. Depending on the location of the primary tumor, there are a number of sensitive organs that will be in the radiation field. Specifically, the most well-studied organs at risk in the context of treating esophageal cancer include the lungs and heart. Radiation pneumonitis is clearly linked to the dose and volume of lung treated. Various single dosimetric parameters have been proposed to estimate the probability of developing radiation pneumonitis after radiotherapy.[428,465–469] Investigators from the Netherlands compared different normal tissue complication probability (NTCP) models to predict radiation pneumonitis.[468] Using the observed incidence of radiation pneumonitis among breast cancer, malignant lymphoma, and inoperable non–small-cell lung cancer (NSCLC) patients, they found that the underlying local dose-effect relation for radiation pneumonitis was linear. This was better represented by the mean lung dose (MLD) model, rather than a step function model represented by a threshold dose such as V20. In their patient population, the MLD was the most accurate predictor for the incidence of radiation pneumonitis. Willner and colleagues[466] performed an analysis of pneumonitis risk from dose volume histogram (DVH) parameters among patients treated with 3D conformal radiotherapy.[466] Their data indicated that it is reasonable to disperse the dose outside the target volume over large areas in order to reduce the volumes of lung receiving >40 Gy. They found that reducing the high-dose volume reduces the pneumonitis rate more than a corresponding reduction in the low-dose regions of the DVH. Additionally, Konski and colleagues[470] were able to correlate cardiac toxicity to dosimetric and patient factors. Specifically they recommended a threshold of V20, V30, and V40 below 70%, 65%, and 60%, respectively, to decrease symptomatic cardiac toxicity. In general, practice a MLD <20 Gy is standard. Cardiac dose constraints are not as clearly defined, but a V30 <35% is reasonable.

In the palliative setting, there are a variety of radiation-treatment regimens.[471] The goal is rapid palliation of symptoms and the most common approach is to treat anteroposteriorly and posteroanteriorly, including the primary tumor with 2-cm margins, in 10 3-Gy fractions to a total dose of 30 Gy.

Treatment of Metastatic Disease

A variety of single-agent and combination chemotherapy regimens have been evaluated in patients with recurrent or metastatic

۰۲۱-۶۶۱۹۸۵۱۴ www.myuptodate.com دریافت آخرین نسخه آپتودیت آفلاین

carcinoma of the esophagus. Phase II clinical trials in this population have identified drugs with activity that have been integrated into combined modality regimens for the treatment of earlier stage disease. Standard criteria for evaluating treatment response require that serial measurement of disease be possible. For the esophageal cancer patient with metastatic disease to distant organ sites or lymph nodes, treatment response can be reliably assessed using spiral CT scans or MRI. The serial tumor measurement for response assessments in patients with disease limited to the esophagus is less reliable. An endoscopy with brushings and biopsy may be performed to confirm a clinically determined complete response; however, a biopsy is subject to sampling error, and biopsy findings are not a reliable indicator of complete histologic resolution of disease. Whole-body FDG-PET performed before and during or after chemotherapy may be a valuable noninvasive method of predicting tumor response and a favorable treatment outcome. Several studies have shown that a reduction in tumor FDG uptake (median decrease in standardized uptake value) correlates with response and longer survival.[154,158,327] Until the mid-1990s, the accumulated experience with chemotherapy was almost entirely in patients with squamous cell tumors. With the rising incidence of adenocarcinoma of the distal esophagus, GEJ, and cardia in the United States and Western industrialized countries, patients with this histologic type now make up more than half of referrals for chemotherapy. Most trials of new agents and combined modality regimens now include patients with both tumor types. Modern chemotherapy trials in advanced disease also treat gastric adenocarcinoma in concert with adenocarcinoma of the GEJ and distal esophagus, and some trials also include squamous esophageal cancer.

Single-Agent Chemotherapy

Studies of single-agent chemotherapy for esophageal cancer are summarized here. Response data for many of the older drugs have come from broad phase I and II trials conducted in the 1970s and 1980s, which included small numbers of esophageal cancer patients.[472–481] Bleomycin, 5-FU, mitomycin, and cisplatin have been used most frequently because of their single-agent activity and additive or synergistic effects with radiation. Because of the potential for pulmonary toxicity, bleomycin is no longer included in combination regimens, having been replaced by 5-FU. Similarly, mitomycin is used less often because of its toxicity profile, which includes hemolytic–uremic syndrome and cumulative myelosuppression.

Seven trials examined the use of cisplatin for single-agent therapy in esophageal cancer patients,[479,482–487] six of which used dosages ranging from 50 to 120 mg/m^2 every 3 to 4 weeks. The cumulative response rate in patients with metastatic or recurrent disease was 21%. Vinorelbine is a semisynthetic vinca alkaloid that has less neurotoxicity than vincristine and vinblastine. Phase II trials in metastatic squamous cell cancer of the esophagus report response rates of 20% to 25% using weekly or biweekly dosing schedules.[488,489] In a subsequent trial, Conroy et al.[490] evaluated the doublet of vinorelbine and cisplatin. A total of 71 patients with metastatic squamous cell cancer were treated, and a 34% response rate was observed. Vinorelbine was evaluated in a phase II trial in 29 patients with adenocarcinoma of the esophagus who had failed prior chemotherapy, with minor activity (7% response rate) observed.[491]

The taxane paclitaxel has been tested in both adenocarcinoma and squamous cell carcinoma of the esophagus. Paclitaxel promotes the stabilization of microtubules and is a cycle-specific agent affecting cells in the G2/M phase. Paclitaxel also enhances radiation effects and may be both concentration and schedule dependent.[492] Three trials of single-agent paclitaxel have been reported. One used the maximum tolerable dose of 250 mg/m^2, derived from initial phase I trials using a 24-hour infusion schedule.[493] The overall response rate was 32% (34% in 33 patients with adenocarcinoma, and 28% in 18 patients with squamous cell carcinoma). The second trial tested a regimen of 140 mg/m^2 infused during 96 hours in patients previously treated using a shorter infusion schedule of paclitaxel-containing combination chemotherapy.[494] No responses were observed. The third trial evaluated single-agent paclitaxel administered by a weekly 1-hour infusion at a dose of 80 mg/m^2 in a large multicenter phase 2 setting.[495] A modest response rate of 15% was observed in 65 patients without prior chemotherapy treatment (16% in the 50 patients treated with adenocarcinoma and 13% in the 15 patients treated with squamous cell carcinoma). Limited activity (5%) was seen in patients with prior chemotherapy. Despite the low response rate, the median survival was 274 days, and toxicity, including hematologic toxicity, was minimal.

Docetaxel was evaluated at a dose of 100 mg/m^2, every 3 weeks in a combined esophageal and gastric cancer trial treating 33 patients with gastric cancer and 8 patients with esophageal adenocarcinoma.[496] Two of the eight patients (25%) with esophageal adenocarcinoma had a major response. Overall, grade 4 neutropenia occurred in 88% of patients and neutropenic fever in 46%. A larger trial of docetaxel 75 mg/m^2 in 22 patients with esophageal adenocarcinoma reported a response rate of 18% in chemotherapy-naïve patients and no responses in previously treated patients.[496] Febrile neutropenia occurred in 32% of patients. A recent trial of 70 mg/m^2 every 3 weeks in 49 patients with squamous cell carcinoma reported a 20% response rate.[497] Eighty-eight percent of patients had grade 3 or 4 neutropenia and 18% had febrile neutropenia.

Drugs that have been adequately tested in squamous cell cancer of the esophagus and have response rates less than 5% are the methotrexate analog dichloromethotrexate[498] and trimetrexate,[499,500] and etoposide,[501,502] ifosfamide,[503,504] and carboplatin.[505,506] A more contemporary study of etoposide in untreated patients with squamous cell carcinoma reported a response rate of 19% (5 of 26 patients).[507] Carboplatin has been studied in both adenocarcinoma and squamous cell carcinoma, and, in contrast to the activity of a single agent, responses to carboplatin were observed in only 3 of 59 chemotherapy-naïve patients. Therefore, substitution of single-agent carboplatin for cisplatin is not recommended when treating patients with either adenocarcinomas or squamous cell carcinomas of the esophagus. Nonetheless, carboplatin combination regimens used as part of combination chemotherapy, in chemoradiation (as previously discussed) and in metastatic disease regimens (discussed later), appear to have comparable activity to cisplatin-based therapy.

Topotecan and gemcitabine have been separately evaluated in both histologic tumor types and have been shown to be inactive.[508–510] The topoisomerase II inhibitor irinotecan has been evaluated in two phase II trials in adenocarcinoma of the stomach and GEJ, with a response rate of 15% observed.[511,512]

Combined-Agent Chemotherapy

Older trials (before the mid-1990s) and those in Europe were almost exclusively limited to patients with squamous cell carcinoma. Because esophageal cancer is a relatively uncommon malignancy, many studies include a heterogeneous population of treatment-naïve patients with locally advanced intrathoracic disease as well as patients with recurrent or metastatic disease. Not only is there variation in the patient population, but more recent trials usually limit eligibility to patients with no prior chemotherapy and performance status of 0 or 1. Thus, in the absence of comparative trials, newer regimens may appear more effective.

Most series consist of small numbers of patients; therefore, the 95% CIs are large and nearly all responses are partial. On average, the duration of response ranges from 3 to 6 months.

Trials conducted in the 1980s testing three-drug regimens such as cisplatin, bleomycin, and vindesine[255,513] and cisplatin and mitoguazone combined with vindesine[514] or vinblastine[515] yielded response rates of 30% to 40% in patients with squamous cell carcinoma. Toxicity was primarily moderate myelosuppression. Bleomycin and

۰۲۱-۶۶۱۹۸۵۱۴ www.myuptodate.com tahir99 - UnitedVRG دریافت آخرین نسخه آپتودیت آفلاین

TABLE 45.9

Randomized Phase II–III Chemotherapy Trials In Esophageal and GE Junction Cancers

Regimen	Patients (N)	Histologic Type	Response Rate (%)	Overall Survival	Reference
C + 5-FU vs C	88	S	35 19	28 wks 33 wks	483
ECF vs FAMTX	274	A	45 21	8.9 mos 5.7 mos	517
ECF vs MCF	690	A/S	42 44	9.4 mos 8.7 mos	518
ECF vs ECX vs EOF vs EOX	1002	A/S	41 46 42 48	9.9 mos 9.9 mos 9.3 mos 11.2 mos	520
5-FU + O vs 5-FU + C	220	A	35 25	10.7 mos 8.8 mos	521
5-FU + C vs Cape + C	316	A	32 46	9.3 mos 10.5 mos	522
5-FU + C vs S-1 + C	1,053	A	32 29	7.9 mos 8.6 mos	524
CF vs DCF	445	A	26 36	8.6 mos 9.2 mos	525
5-FU + O +/− D	143	A	49 28	17.3 mos 14.5 mos	526
5-FU + C vs 5-FU + Irino	333	A	26 32	8.7 mos 9.0 mos	549

C, cisplatin; S, squamous cell carcinoma; ECF, epirubicin/cisplatin; FAMTX, 5-FU/doxorubicin/methotrexate; A, adenocarcinoma; EOX, epirubicin/cisplatin or oxaliplatin/5-FU or capecitabine; O, oxaliplatin; Cape, capecitabine; D, docetaxel; Irino, irinotecan.

mitoguazone were subsequently replaced by 5-FU to reduce toxicity and to take advantage of its synergistic activity with cisplatin.

The two-drug combination of cisplatin (100 mg/m^2 on day 1) and 5-FU (1,000 mg/m^2 per day continuous infusion for 96 to 120 hours) has been the standard regimen for 2 decades to treat patients with either squamous cell carcinoma or adenocarcinoma. A 35% response rate was observed in patients with metastatic, recurrent, or locally advanced incurable squamous cell cancer of the esophagus.[483] Higher response rates (in the 40% to 60% range) were reported in trials administering two or three cycles of cisplatin and 5-FU as induction therapy before surgery. The difference in response rates may be related to better performance status, better nutrition, and smaller volume disease in the surgical candidates. Despite the common use in the oncology community of the combination of 5-FU and cisplatin for the treatment of esophageal carcinoma, only one trial conducted by the EORTC has directly addressed the issue of the comparative efficacy of single-agent cisplatin and the combination of 5-FU and cisplatin (Table 45.9).[483] Patients with locally advanced or metastatic squamous cell carcinoma were randomly assigned to receive either cisplatin (100 mg/m^2) plus continuous-infusion 5-FU (1,000 mg/m^2 per day, days 1 to 5) or to cisplatin (100 mg/m^2) alone, with both regimens repeated every 3 weeks. The cisplatin/5-FU arm had a higher response rate (35%) and better median survival (33 weeks) than the cisplatin arm (19% and 28 weeks, respectively), but these findings were not statistically significant. Cisplatin/5-FU was also more toxic, with 16% treatment-related deaths for the combination.

Cisplatin in combination with tegafur uracil (UFT), an oral 5-FU pro-drug combining tegafur with uracil, an inhibitor of the enzyme dihydropyrimidine dehydrogenase that degrades 5-FU, has also been evaluated in esophageal cancer. A response rate of 46% was reported.[516]

Recent phase III trials have compared the addition of a third agent to cisplatin/5-FU versus cisplatin/5-FU alone. The Royal Marsden group developed the ECF regimen, a combination of epirubicin (50 mg/m^2) and cisplatin (60 mg/m^2) every 3 weeks in combination with daily protracted continuous infusion 5-FU (200 mg/m^2 per day) in gastric cancer. The ECF regimen was compared in a phase III trial in gastric and GEJ adenocarcinoma with a bolus regimen of 5-FU, doxorubicin, and methotrexate (FAMTX) (see Table 45.9).[517] The ECF regimen resulted in a superior response rate (45% versus 21%), failure-free survival (7.4 months versus 3.4 months), and median survival (8.9 months versus 5.7 months) in comparison with FAMTX. The ECF regimen had a tolerable toxicity profile, with less than 10% rates of grade 3 or 4 diarrhea or stomatitis. A more recent trial treating nearly 600 patients with advanced esophageal squamous and adenocarcinoma and gastric adenocarcinoma compared the ECF regimen with a similar regimen substituting mitomycin (7 mg/m^2 every 6 weeks) for epirubicin (see Table 45.9).[518] This trial validated the previously reported response rate and median survival for the ECF regimen (42%, 9.4 months), but the response rate and median survival observed for the mitomycin combination regimen (44%, 8.7 months) were identical to those of ECF. Given that there was no difference in efficacy for the epirubicin- versus mitomycin-containing arms, this study raises the question of whether or not the addition of a third agent makes a difference in outcome when combined with cisplatin and protracted infusion 5-FU. Of the 533 patients enrolled in this trial, 40 had squamous cell carcinoma of the esophagus and the remainder had adenocarcinoma (125, esophagus; 125, gastroesophageal

۰۲۱-۶۶۱۹۸۵۱۴ www.myuptodate.com دریافت آخرین نسخه آپتودیت آفلاین

junction; 243, stomach). There was a significantly higher response rate among patients with GEJ cancers than among those with distal gastric cancers (48% versus 37%).

Oxaliplatin, as a potential substitute for cisplatin, and oral capecitabine, as a substitute for 5-FU, have been explored in phase II trails[519] and, more recently, phase III randomized trials in esophageal and gastric adenocarcinoma (see Table 45.9). Cunningham et al.[520] reported results of a 1,000 patient phase III trial in esophageal squamous cell and adenocarcinoma and gastric cancer, evaluating the frontline use of oxaliplatin or capecitabine. This trial compared conventional ECF with the substitution of capecitabine for infusional 5-FU, and oxaliplatin for cisplatin. The trial employed a two-by-two design, with the control arm ECF, and the experimental arms including capecitabine (625 mg/m^2 twice daily) substituted for infusional 5-FU; oxaliplatin (130 mg/m^2) substituted for cisplatin; and a fourth arm with a substitution of both capecitabine and oxaliplatin. Capecitabine was found to be noninferior to 5-FU, and oxaliplatin noninferior to cisplatin, with comparable rates of antitumor response and progression-free survival across the four treatment arms. A toxicity analysis favored oxaliplatin over cisplatin for neutropenia, alopecia, renal toxicity, and thromboembolism. In a planned comparison of ECF to EOX (epirubicin, oxaliplatin, capecitabine), median survival was superior for EOX (11.2 months versus 9.9 months; HR, 0.80; $p = 0.02$). A second phase III trial from the German AIO group compared infusional 5-FU (24-hour infusion) plus leucovorin combined with either oxaliplatin (85 mg/m^2) or cisplatin (50 mg/m^2) once every 2 weeks in 220 patients with metastatic gastroesophageal adenocarcinoma.[521] Like the Cunningham et al. trial, oxaliplatin was found to be noninferior to cisplatin. Oxaliplatin caused significantly less nausea and vomiting, fatigue, renal toxicity, and thromboembolism. Remarkable on both arms of this trial was the relatively low level of grade 3 or 4 toxicities in all categories, running less than 10% to 15%, which was likely due to the 2 weekly schedule of chemotherapy mimicking colorectallike cancer scheduling of chemotherapy. Response rates (24.5% to 34.8%), progression-free (3.9 months versus 5.8 months), and overall survival (8.8 months versus 10.7 months) were comparable between the two treatment arms, although all end points trended higher on the oxaliplatin arm. Lastly, a third phase III trial reported by Kang et al.[522] compared capecitabine (1,000 mg/m^2) twice a day for 14 days to 5-FU (800 mg/m^2 per day continuous infusion) for 5 days, cycled every 3 weeks with cisplatin (80 mg/m^2). Like the Cunningham et al. trial, capecitabine was found to be noninferior to 5-FU. Rates of toxicity on the treatment arms were similar, as were measures of progression-free (5.0 months versus 5.6 months) and overall survival (9.3 months versus 10.5 months). Based on the results of these three phase III trials, the substitution of oxaliplatin for cisplatin, or capecitabine for 5-FU, seems justified. The two-drug regimens in the Al-Batran et al.[521] and Kang et al.[522] trials had favorable toxicity profiles and efficacy compared to the three drug regimens of Cunningham et al., and whether or not epirubicin is required as part of therapy in metastatic disease is unclear.

An alternative oral 5-FU agent, S-1, combines the 5-FU prodrug tegafur with a bowel protectant (oteracil) and an inhibitor of dihydropyrimidine dehydrogenase (gimeracil). A phase III trial conducted in Japan evaluated S-1 40 to 60 mg twice a day for 3 weeks as a single agent, versus S-1 plus cisplatin (60 mg/m^2), cycled once every 5 weeks, in advanced gastric cancer. S-1 plus cisplatin was superior to S-1 alone, with improved rates of response (54% versus 31%), progression-free (6 months versus 4 months), and overall survival (13 months versus 11 months).[523] Based on encouraging data for S-1, a phase III superiority trial comparing S-1 50 mg/m^2 in two daily divided doses for 21 days was compared to infusional 5-FU 1,000 mg/m^2 per day for 5 days, cycled every 28 days (see Table 45.9).[524] Both arms were combined with cisplatin, with a lower dose of cisplatin combined with S-1 (75 mg/m^2) compared to the 5-FU arm (100 mg/m^2). A lower dose of S-1 than that used in the Japanese trials was mandated due to greater toxicity for S-1 reported in Western patients in prior phase I and II trials. The trial failed to demonstrate superiority for the S-1 arm, with equivalent rates of overall survival (7.9 months versus 8.6 months). The S-1 arm had less toxicity than 5-FU, but the lesser cisplatin dose likely accounted for much of the toxicity differences between the treatment arms. Whether S-1 will be adopted in practice in Western countries has yet to be established.

The addition of docetaxel as a third agent added to 5-FU and cisplatin has also recently been reported in a phase III trial of GEJ and gastric cancer (see Table 45.9). 5-FU dosed at 1,000 mg/m^2 by continuous infusion during 5 days combined with cisplatin (100 mg/m^2) was compared with cisplatin (75 mg/m^2), 5-FU (750 mg/m^2) by continuous infusion during 5 days, and docetaxel (75 mg/m^2) in 445 patients with metastatic gastric or GEJ adenocarcinoma.[525] Docetaxel resulted in a higher response rate and time to progression (36%, 5.6 months) compared with 5-FU and cisplatin (26%, 3.7 months), but only a marginal median survival improvement (0.6 months) was noted for three-drug therapy. Toxicity was substantial in both treatment arms, including hematologic and gastrointestinal toxicity, with 80% of patients receiving the three-drug combination experiencing grade 3 or 4 neutropenia. The recent trials of 5-FU infusion combination chemotherapy indicate improved therapy tolerance and potentially enhanced antitumor activity, employing either a once every 2 week or a more protracted infusion of 5-FU as in the ECF regimen. The addition of a third agent, including epirubicin or docetaxel, to 5-FU and cisplatin may modestly increase response rates and survival, but, in the case of docetaxel combination therapy, may result in substantial therapy-related toxicity. The use of relatively high and relatively toxic doses of cisplatin (75 to 100 mg/m^2) is also called into question, given data from the British phase III ECF trials that indicate potential better therapy tolerance for 60 mg/m^2 without evident compromising of treatment efficacy. The tolerance of a three-drug regimen may also be influenced by patient age. In a phase III trial targeting 143 patients with esophagogastric cancer 65 years or older, Al-Batran and colleagues[526] compared a regimen of biweekly infusional 5-FU and oxaliplatin with or without the addition of docetaxel (see Table 45.9). A higher response rate was reported for triplet therapy with no impact on overall survival, and resulted in much higher rates of toxicity and an actual detriment in quality of life measures compared to two-drug therapy.

Five trials using interferon-α_{2a} (IFN-α_{2a}) as a biomodulator of 5-FU suggested possible benefit.[527–531] These phase 2 trials combined IFN-α_{2a} with 5-FU and with cisplatin combined with continuous-infusion 5-FU, with response rates reported ranging from 27% to 50%, with a suggestion of higher response rates seen in squamous cell carcinoma. Etoposide and cisplatin with or without 5-FU have also undergone a phase II evaluation.[532–534] Combination regimens that include paclitaxel have been evaluated in esophageal cancer patients. In three phase II trials of paclitaxel and cisplatin, response rates ranged from 43% to 50%; activity was comparable in both histologic tumor types, often with severe hematologic toxicity.[535–537] A phase I trial of weekly carboplatin dosed from an area under the curve of 2 to 5 combined with a 1-hour infusion of paclitaxel, 100 mg/m^2, in 40 patients with advanced esophageal and GEJ cancer had an overall response rate of 54%.[538]

The three-drug combination of paclitaxel (175 mg/m^2, 3-hour infusion), combined with cisplatin (20 mg/m^2 daily days 1–5) and 5-FU (1,000 mg/m^2 per day continuous infusion × 120 hours) was evaluated in a multicenter 60 patient trial.[539] A 48% response rate was reported (56% in patients with squamous cell cancer and 46% in patients with adenocarcinoma). Toxicity resulted in unplanned hospitalizations for 48% of patients.

Although the dose and schedule of paclitaxel in combination with other active drugs varies among phase II trials, shorter infusion schedules of paclitaxel, in particular the weekly 1-hour schedule, result in less myelotoxicity.

Other regimens of interest include those containing irinotecan. First reported was the doublet of irinotecan and cisplatin administered in low dose on a weekly schedule.[540] In vitro studies demonstrated sequence-dependent synergy for cisplatin followed by irinotecan, which prevents the removal of cisplatin-induced DNA interstrand cross-links. Two trials yielded encouraging results (51% to

۰۲۱-۶۶۱۹۸۵۱۴ www.myuptodate.com tahir99 - UnitedVRG دریافت آخرین نسخه آپتودیت آفلاین

57% response) with a regimen of cisplatin (30 mg/m^2) followed by irinotecan (65 mg/m^2) administered weekly for 4 weeks, repeated every 6 weeks in adenocarcinoma and squamous cancer.[540,541] Dysphagia and global quality of life were improved in the majority of patients in one of these trials.[540] In both studies, toxicity consisted of myelosuppression, diarrhea, and fatigue. Irinotecan 50 mg/m^2 combined with weekly cisplatin 25 mg/m^2 and docetaxel 30 mg/m^2, days 1 and 8 every 21 days, was studied in a phase II trial in 39 patients with esophagogastric cancer.[542] An encouraging response rate of 54% was observed, with tolerable rates of grade 3 and 4 neutropenia (21%) and diarrhea (26%). However, a recent randomized phase II trial reported only in abstract form compared the chemotherapy regimens FOLFOX, irinotecan and cisplatin, and ECF, all combined with the EGFR-targeted agent cetuximab (Table 45.10).[543] The FOLFOX and ECF arms had similar response rates and overall survival, and the toxicity analysis favored the FOLFOX arm, and has led to further questioning of the contribution of epirubicin to a two-drug combination of oxaliplatin and a fluorinated pyrimidine. Notable, however, was the inferior performance of the irinotecan–cisplatin arm, which had the lowest rates of response and overall survival.

Recent studies exploring non–cisplatin-containing combination regimens have employed the taxanes and irinotecan. Although these trials have indicated encouraging response rates in the phase II setting, substantial hematologic and diarrheal toxicities of these regimens may not offer an advantage over the older cisplatin-containing regimens.[544–548] Docetaxel has been evaluated in combination with irinotecan in four recent phase II trials. Two trials evaluated irinotecan doses of 100 to 160 mg/m^2 and docetaxel doses of 50 to 60 mg/m^2 administered once every 3 weeks. Two trials evaluated the day 1 and day 8 schedule of irinotecan (50 to 55 mg/m^2) and docetaxel (25 to 35 mg/m^2) cycled every 3 weeks. Response rates range from 13 to 30 hematologic toxicity, which exceeded 50% in patients treated on the schedule of once every 3 weeks, seemed to be less using the day 1 and day 8 schedule compared with the once every 3 weeks schedule.

A phase III comparison of cisplatin and infusional 5-FU to the combination of irinotecan and infusional 5-FU was recently reported in advanced esophagogastric cancer (see Table 45.9).[549] Response rates (25.8% to 31.8%) and progression-free (4.2 months versus 5.0 months), and overall survival (8.7 months versus 9.0 months) were comparable for the two regimens. Toxicity favored the irinotecan 5-FU arm. Data from this trial and the oxaliplatin-based studies conducted in Europe have led to greater utilization of both irinotecan and oxaliplatin in combination with infusional 5-FU for the treatment of advanced esophagogastric cancer at European centers.

Docetaxel and either vinorelbine or capecitabine were evaluated in phase II trials in squamous cell carcinoma[550,551] with response rates of 46% to 60%. In summary, recent trials of combination regimens that include paclitaxel or irinotecan appear to have comparable response rates to previous regimens; however, the duration of response remains brief. In addition, the toxicities recorded in some of these phase II single-institution experiences have been excessive.

Targeted Agents

Phase III trials of targeted agents studied alone or in combination with chemotherapy are outlined in Table 45.10. Validation of the activity of a growth factor receptor–targeted agent, trastuzumab, was recently achieved in esophagogastric cancer (see Table 45.10).[552] Over 3,800 patients with gastric or GEJ adenocarcinoma were screened for overexpression of the HER2 receptor by fluorescence in situ hybridization (FISH) and immunohistochemistry; 22.1% tested positive. Five hundred ninety-four patients were ultimately randomized to chemotherapy alone with (1) capecitabine 1,000 mg/m^2 twice a day for 14 days or (2) infusional 5-FU 800 mg/m^2 per day for 5 days, combined with cisplatin 80 mg/m^2 on day 1, cycled every 3 weeks, or to chemotherapy plus trastuzumab 6 mg/kg once every 3 weeks. The majority of patients received capecitabine plus cisplatin as the chemotherapy regimen. All end points were improved with the addition of trastuzumab to chemotherapy, including antitumor response (47.3% versus 34.5%), progression-free survival (6.7 months versus 5.5 months), and overall survival (13.8 months versus 11.1 months) (HR, 0.74; $p = 0.0046$). Toxicity was comparable for the two

TABLE 45.10

Phase II–III Randomized Trials of Targeted Agents

Regimen	Patients (N)	Histologic Type	Response Rate (%)	Overall Survival (months)	Reference
Cape-C +/− trastuzumab	584	A	47 35	13.8 11.1	552
FOLFOX vs Irino-C vs ECF + cetuximab	210	A/S	54 46 58	12.4 8.9 11.5	561
EOX +/− panitumumab	553	A	46 42	8.8 11.3	562
Cape-C +/− cetuximab	904	A	29 29	10 10	563
5-FU–C +/− cetuximab	62	S	19 13	9.5 5.5	564
Cape-C +/− bevacizumab	774	A	46 37	12.1 10.1	566
Ramucirumab vs placebo	355	A	3 3	5.2 3.8	567
Everolimus vs placebo	656	A	4 2	5.4 4.3	568

Cape, capecitabine; C, cisplatin; A, adenocarcinoma; FOLFOX, 5-FU + oxaliplatin; Irino-C, irinotecan-cisplatin; ECF, epirubicin/cisplatin; S, squamous cell carcinoma; EOX, epirubicin/cisplatin or oxaliplatin/5-FU or capecitabine.

۰۲۱-۶۶۱۹۸۵۱۴ www.myuptodate.com دریافت آخرین نسخه آپتودیت آفلاین

treatment arms, with no significant cardiotoxicity from trastuzumab other than an asymptomatic, less than 10% drop in left ventricular ejection fraction, which was slightly higher on the trastuzumab arm compared to chemotherapy alone (4.6% versus 1.1%). Based on these results, the inclusion of trastuzumab in the first-line treatment of HER2+ metastatic esophagogastric cancer should now be considered. Based on these data and pilot data combining trastuzumab with chemoradiotherapy in esophageal cancer RTOG has undertaken a phase III trial (RTOG-1010) comparing preoperative chemoradiotherapy with carboplatin and paclitaxel with or without trastuzumab in locally advanced adenocarcinoma of the esophagus and GEJ, as discussed previously.

In patients with localized esophageal adenocarcinoma, HER2+ disease was associated with a significantly lower tumor grade, earlier stage of disease with fewer malignant lymph nodes, and the presence of Barrett's esophagus. These features of HER2+ localized esophageal cancer led to an independent improvement in disease-specific survival (HR, 0.54; 95% CI, 0.35 to 0.84) and overall survival ($p = 0.0022$), suggesting that HER2+ is a favorable prognostic feature in localized esophageal adenocarcinoma.[553]

With evidence for effectiveness of agents targeting the EGFR in NSCLC (including receptor-associated tyrosine-kinase inhibitors) and in colorectal cancer (including monoclonal antibodies blocking the binding of the EGFR ligand), recent phase II trials have evaluated EGFR-targeted agents in esophageal squamous cell and adenocarcinoma. A recent phase II trial of the EGFR tyrosine-kinase inhibitor gefitinib failed to indicate activity for esophageal adenocarcinoma, but limited activity was observed in squamous cell cancer.[554] A second trial indicated some limited activity for adenocarcinoma,[555] but in both trials, most patients experienced early disease progression. A phase II trial of the EGFR tyrosine-kinase inhibitor erlotinib reported a 9% response rate in 44 patients with adenocarcinoma of the GEJ.[556] With these mixed phase II trial results, a recent negative trial for an EGFR tyrosine-kinase inhibitor was reported only in abstract form by Dutton et al.[557] The trial compared best supportive care to treatment with gefitinib in patients with esophageal and GEJ adenocarcinomas progressing on conventional chemotherapy. In this large trial, no difference in overall survival could be demonstrated for gefitinib compared to supportive care alone.

Monoclonal antibodies targeting the EGFR, including cetuximab and panitumumab, have proceeded to phase III trial investigation combined with chemotherapy, based on promising data from phase II trials.[558–560] The randomized phase II trial conducted by the CALGB and ECOG evaluated three modern chemotherapy regimens combined with cetuximab in the first-line treatment of esophageal and GEJ cancer (see Table 45.10),[561] and was discussed previously. The regimens used were weekly irinotecan–cisplatin, ECF, and FOLFOX (5-FU, leucovorin, and oxaliplatin). The trial indicated comparable response rates, progression-free survival, and overall survival for the FOLFOX and ECF plus cetuximab arms, whereas the irinotecan–cisplatin arm was inferior. The final results of this study may not contribute much to the debate about EGFR-targeted agents, because two large phase III trials of these agents combined with chemotherapy failed to improve outcomes. Waddell and colleagues[562] reported results of the REAL-3 trial in esophagogastric cancer, comparing patient treatment with EOX with or without the EGFR antibody panitumumab (see Table 45.10).[562] In the 553 patients treated, although response rates for treatment with or without panitumumab were similar, overall survival was significantly inferior on the panitumumab arm (11.3 versus 8.8 months) and progression-free survival trended inferior for panitumumab (7.4 versus 6.0 months). Toxicity rates were higher on the panitumumab arm, and the chemotherapy starting doses were lower with panitumumab than on the chemotherapy alone arm. Prognostic biomarkers studied on the trial included *KRAS* mutation, *PIK3CA* kinase mutation, and loss of phosphatase and tensin homolog (PTEN). These markers were affected in a tiny minority of patients, and no clear biomarker has emerged from this trial. The potential deleterious effect of adding an EGFR antibody to the treatment of esophagogastric cancer was also seen in a recent chemoradiotherapy trial, discussed earlier, in which adding cetuximab to definitive chemoradiotherapy in esophageal cancer also appeared to worsen outcomes.[349] A second negative trial for EGFR-targeted antibodies in advanced disease was reported by Lordick et al. (see Table 45.10).[563] The 904 patients with esophagogastric cancer were randomized to treatment with capecitabine and cisplatin with or without cetuximab. Progression-free survival and overall survival also trended inferior on the cetuximab arm (progression-free survival, 5.6 versus 4.4 months; overall survival, 10.7 versus 9.4 months), and response rates were identical (29%). In contrast to these negative trials, Lorenzen et al.[564] reported results of a small phase II trial in advanced squamous cancer of the esophagus comparing 5-FU–cisplatin with or without cetuximab (see Table 45.10). Outcomes were poor on both arms of the trial; however, response rates and overall survivals were improved on the cetuximab arm (19% versus 13%; 9.5 months versus 5.5 months). A larger phase III trial in squamous cancer of the esophagus is now ongoing (NCT01627379) to evaluate panitumumab combined with 5-FU and cisplatin. RTOG-0436, adding cetuximab to primary chemoradiotherapy in locally advanced esophageal cancer,[350] was discussed earlier, and was also a negative trial for the addition of EGFR-targeted therapy.

Another growth factor receptor pathway under active investigation is the vascular endothelial growth factor (VEGF) receptor pathway, based on trials that demonstrate improved effectiveness for chemotherapy in colorectal cancer when combined with the anti–VEGF-A ligand monoclonal antibody bevacizumab. A recent phase II trial combined bevacizumab at a dose of 15 mg/kg every 3 weeks in combination with a day 1 and day 8 schedule of irinotecan (65 mg/m^2) and cisplatin (30 mg/m^2).[565] The multicenter trial treated 47 patients treated with metastatic adenocarcinoma of the GEJ and more distal gastric cancer. An encouraging response rate of 65% was observed, with a suggestion of improvement in time to tumor progression (8.9 months) compared with historical controls. A phase III trial combining bevacizumab with either 5-FU or capecitabine plus cisplatin in 774 patients with esophagogastric adenocarcinoma was recently reported by Ohtsu and colleagues (see Table 45.10).[566] Despite improvements in progression-free survival (5.3 to 6.7 months) and response rate (37% to 46%), a trend toward improvement in overall survival did not reach statistical significance (10.1 to 12.1 months; HR, 0.87; $p = 0.1002$). Another VEGF-targeted agent, ramucirumab, which blocks ligand binding to the receptor VEGF2, indicated a positive effectiveness in refractory esophagogastric cancer compared to placebo.[567] Fuchs and colleagues[567] randomized 355 patients progressing on 5-FU or platinum-based chemotherapy to best supportive care plus placebo versus best supportive care plus ramucirumab administered once every 2 weeks. Although no significant antitumor responses were seen, overall survival was significantly improved with ramucirumab (3.8 to 5.2 months) and toxicity was limited to a slight increase in hypertension. Results for studies of the combination of ramucirumab with chemotherapy in first- or second-line treatment are pending publication. The positive results for ramucirumab have led to a resurgent interest in the study of VEGF-targeted agents in esophageal cancer.

Finally, a recent large, placebo-controlled trial in chemotherapy refractory esophagogastric cancer compared placebo to the mammalian target of rapamycin (mTOR)–targeted agent everolimus in 656 patients (see Table 45.10).[568] Although progression-free survival was slightly improved with everolimus, there was no improvement in overall survival (5.4 months for everolimus versus 4.3 months for placebo).

STAGE-DIRECTED TREATMENT RECOMMENDATIONS

Although level I evidence is lacking to support ironclad recommendations regarding the most effective treatment of patients

۰۲۱-۶۶۱۹۸۵۱۴ www.myuptodate.com tahir99 - UnitedVRG دریافت آخرین نسخه آپتودیت آفلاین

grouped by stage in many clinical situations, reasonable trial-generated information exists to suggest appropriate therapeutic interventions for patients grouped under broad staging categories.

Resection remains the standard by which all other treatment options must be measured for patients with high-grade dysplasia in the setting of Barrett's esophagus or T1 disease limited to the mucosa, with the caveat that esophagectomy-associated mortality must be extremely low. EMR may be considered an appropriate first step in addressing patients with mucosa-limited lesions. Intensive long-term endoscopic surveillance for patients with Barrett's esophagus–associated high-grade dysplasia is necessary to limit both cancer- and treatment-related mortality.

An esophagectomy is an appropriate method for treating patients with stage I, II, and III disease. Alternatively, definitive chemoradiation is a therapeutic option for patients with stage II and III disease, especially those who are not considered surgical candidates or who have squamous cell carcinoma at or above the carina. The high rate of persistent or recurrent local–regional disease after definitive chemoradiation suggests that additional local therapy in the form of surgery may be necessary and beneficial. This potential benefit may be realized only if perioperative mortality is minimized. Preoperative chemoradiation has been proven to be more effective than surgery alone, and is now appropriately embraced by US oncologists for patients with resectable stage IIB and III esophageal cancers. Defining more effective regimens must continue to be the focus of well-designed clinical trials. Postoperative chemoradiation should be reserved for patients with resected adenocarcinoma of the GEJ. Preoperative chemotherapy is an accepted standard of care in the United Kingdom but is still considered investigational in the United States. All patients with unresectable or stage IV disease are ideally suited for clinical trials exploring novel therapeutic agents and approaches.

SELECTED REFERENCES

The full reference list can be accessed at lwwhealthlibrary.com/oncology.

3. Howlader N, Noone AM, Krapcho M, et al. (eds). SEER Cancer Statistics Review, 1975–2010. Bethesda, MD: National Cancer Institute. SEER Web site. http://seer.cancer.gov/csr/1975_2010/. April 2013.
4. Siegel R, Naishadham D, Jemal A. Cancer Statistics, 2013. *CA Cancer J Clin* 2013;63:11–30.
9. Cook MB, Shaheen NJ, Anderson LA, et al. Cigarette smoking increases risk of Barrett's esophagus: an analysis of the Barrett's and Esophageal Adenocarcinoma Consortium. *Gastroenterology* 2012;142:744–753.
16. Bravi F, Edefonti V, Randi G, et al. Dietary patterns and the risk of esophageal cancer. *Ann Oncol* 2012;23:765–770.
22. Edelstein ZR, Farrow DC, Bonner MP, et al. Central adiposity and risk of Barrett's esophagus. *Gastroenterology* 2007;133:403–411.
24. Lagergren J. Influence of obesity on the risk of esophageal disorders. *Nat Rev Gastroenterol Hepatol* 2011;8:340–347.
25. Lagergren J, Bergstrom R, Lindgren A, et al. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. *N Engl J Med* 1999;340:825–831.
26. Chow WH, Finkle WD, McLaughlin JK, et al. The relation of gastroesophageal reflux disease and its treatment to adenocarcinomas of the esophagus and gastric cardia. *JAMA* 1995;274:474–477.
27. Islami F, Kamangar F. *Helicobacter pylori* and esophageal cancer risk: a meta-analysis. *Cancer Prev Res (Phila)* 2008;1:329–338.
31. Spechler SJ. Clinical practice. Barrett's esophagus. *N Engl J Med* 2002; 346:836–842.
33. Spechler SJ. Barrett esophagus and risk of esophageal cancer: a clinical review. *JAMA* 2013;310:627–636.
35. Bhat S, Coleman HG, Yousef F, et al. Risk of malignant progression in Barrett's esophagus patients: results from a large population-based study. *J Natl Cancer Inst* 2011;103:1049–1057.
36. Hvid-Jensen F, Pedersen L, Drewes AM, et al. Incidence of adenocarcinoma among patients with Barrett's esophagus. *N Engl J Med* 2011;365:1375–1383.
40. Spechler SJ, Sharma P, Souza RF, et al. American Gastroenterological Association. American Gastroenterological Association medical position statement on the management of Barrett's esophagus. *Gastroenterology* 2011;140:1084–1091.
41. Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. *Am J Gastroenterol* 2013;108:308–328.
42. Evans JA, Early DS, Fukami N, et al. Standards of Practice Committee of the American Society for Gastrointestinal Endoscopy. The role of endoscopy in Barrett's esophagus and other premalignant conditions of the esophagus. *Gastrointest Endosc* 2012;76:1087–1094.
43. Spechler SJ, Lee E, Ahnen D, et al. Long-term outcome of medical and surgical therapies for gastroesophageal reflux disease: follow-up of a randomized controlled trial. *JAMA* 2001;285:2331–2338.
46. Ferguson MK, Durkin A. Long-term survival after esophagectomy for Barrett's adenocarcinoma in endoscopically surveyed and nonsurveyed patients. *J Gastrointest Surg* 2002;6:29–35.
52. Faybush EM, Sampliner RE. Randomized trials in the treatment of Barrett's esophagus. *Dis Esophagus* 2005;18:291–297.
53. Singh S, Garg SK, Singh PP, et al. Acid-suppressive medications and risk of oesophageal adenocarcinoma in patients with Barrett's oesophagus: a systematic review and meta-analysis. *Gut* 2013;Nov 12 [Epub ahead of print].
54. Haggitt RC. Barrett's esophagus, dysplasia, and adenocarcinoma. *Hum Pathol* 1994;25:982–993.
59. Heath E, Canto MI, Piantadosi S, et al. Secondary chemoprevention of Barrett's esophagus with celecoxib: results of a randomized trial. *J Natl Cancer Inst* 2007;99:545–557.
81. Siewert JR, Feith M, Werner M, et al. Adenocarcinoma of the esophagogastric junction. Results of surgical therapy based on anatomic-topographic classification in 1,002 consecutive patients. *Ann Surg* 2000;232:353–361.
86. Dulak AM, Schumacher SE, van Lieshout J, et al. Gastrointestinal adenocarcinomas of the esophagus, stomach, and colon exhibit distinct patterns of genome instability and oncogenesis. *Cancer Res* 2012;72:4383–4393.
87. Dulak AM, Stojanov P, Peng S, et al. Exome and whole genome sequencing of esophageal adenocarcinoma identifies recurrent driver events and mutational complexity. *Nat Genet* 2013;5:478–486.
88. Agrawal N, Jiao Y, Bettegowda C, et al. Comparative genomic analysis of esophageal adenocarcinoma and squamous cell carcinoma. *Cancer Discov* 2012;2:899–905.
90. Edge SB, Byrd DR, Compton CC, et al. American Joint Commission on Cancer. *AJCC Cancer Staging Manual*. 7th ed. New York: Springer-Verlag; 2009.
101. Ilson DH, Minsky BD, Ku GY, et al. Phase 2 trial of induction and concurrent chemoradiotherapy with weekly irinotecan and cisplatin followed by surgery for esophageal cancer. *Cancer* 2012;118:2820–2827.
105. Kelsen DP, Ginsberg R, Pajak RF, et al. Chemotherapy followed by surgery compared with surgery alone for localized esophageal cancer. *N Engl J Med* 1998;339:1979–1984.
106. Medical Research Council Oesophageal Cancer Working Group. Surgical resection with or without preoperative chemotherapy in oesophageal cancer: a randomised controlled trial. *Lancet* 2002;359:1727–1733.
107. Urba SG, Orringer MB, Turrisi A, et al. Randomized trial of preoperative chemoradiation versus surgery alone in patients with locoregional esophageal carcinoma. *J Clin Oncol* 2001;19:305–313.
110. Arnott SJ, Duncan W, Gignoux M, et al. Preoperative radiotherapy in esophageal carcinoma: a meta-analysis using individual patient data (Oesophageal Cancer Collaborative Group). *Int J Radiat Oncol Biol Phys* 1998;41:579–583.
112. Kelsen DP, Winter KA, Gunderson LL, et al. Long-term results of RTOG Trial 8911 (USA Intergroup 113): a random assignment trial comparison of chemotherapy followed by surgery compared with surgery alone for esophageal cancer. *J Clin Oncol* 2007;25:3719–3725.
113. Allum WH, Stenning SP, Bancewicz J, et al. Long term results of a randomized trial of surgery with or without preoperative chemotherapy in esophageal cancer. *J Clin Oncol* 2009;27:5062–5067.
114. Cooper JS, Guo MD, Herskovic A, et al. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85–01). Radiation Therapy Oncology Group. *JAMA* 1999;281:1623–1627.
116. Bedenne L, Michel P, Bouche O, et al. Chemoradiation followed by surgery compared to chemoradiation alone in squamous cancer of the esophagus: FFCD 9102. *J Clin Oncol* 2007;25:1160–1168.
117. Stahl M, Stuschke M, Lehmann N, et al. Chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma of the esophagus. *J Clin Oncol* 2005;23:2310–2317.
151. Jost C, Binek J, Schuller JC, et al. Endosonographic radial tumor thickness after neoadjuvant chemoradiation therapy to predict response and survival in patients with locally advanced esophageal cancer: a prospective multicenter phase II study. Swiss Group for Clinical Cancer Research (SAKK 75/02). *Gastrointest Endosc* 2010;7:1114.
152. Flamen P, van Cutsem E, Lerut T, et al. The utility of positron emission tomography with 18F-fluorodeoxyglucose (FDG-PET) to predict the pathologic response and survival of esophageal cancer after preoperative chemoradiation therapy (CRT). *Proc Am Soc Clin Oncol* 2001;20:127a.
157. Ott K, Weber WA, Lordick F, et al. Metabolic imaging predicts response, survival, and recurrence in adenocarcinomas of the esophagogastric junction. *J Clin Oncol* 2006;24:4692–4698.

۰۲۱-۶۶۱۹۸۵۱۴ www.myuptodate.com دریافت آخرین نسخه آپتودیت آفلاین

159. Lordick F, Ott K, Krause BJ, et al. PET to assess early metabolic response and to guide treatment of adenocarcinoma of the oesophagogastric junction: the MUNICON phase II trial. *Lancet Oncol* 2007;8:797–805.
160. zum Büschenfelde CM, Herrmann K, Schuster T, et al. 18F-FDG PET-guided salvage neoadjuvant radiochemotherapy of adenocarcinoma of the esophagogastric junction: the MUNICON II trial. *J Nucl Med* 2011;52:1189–1196.
161. Klaeser B, Nitzsche E, Schuller JC, et al. Limited predictive value of FDG-PET for response assessment in the preoperative treatment of esophageal cancer: results of a prospective mutli-center trial (SAKK 75/01). *Onkologie* 2009;32:724–730.
162. Rebollo Aguirre AC, Ramos-Font C, Villegas Portero R, et al. 18F-fluorodeoxiglucose positron emission tomography for the evaluation of neoadjuvant therapy response in esophageal cancer: systematic review of the literature. *Ann Surg* 2009;250:247–254.
163. Kwee R. Prediction of tumor response to neoadjuvant therapy in patients with esophageal cancer with the use of 18F FDG PET: a systematic review. *Radiology* 2010;254:707–717.
170. Rizk N, Venkatraman E, Park B, et al. The prognostic importance of the number of involved lymph nodes in esophageal cancer: implications for revisions of the American Joint Committee on Cancer staging system. *J Thorac Cardiovasc Surg* 2005;132:1374–1381.
172. Rice TW, Rusch VW, Ishwaran H, et al. Cancer of the esophagus and esophagogastric junction: data-driven staging for the seventh edition of the American Joint Committee on Cancer/International Union Against Cancer Cancer Staging Manuals. Worldwide Esophageal Cancer Collaboration. *Cancer* 2010;116:3763–3773.
173. Merkow RP, Bilimoria KY, McCarter MD. Use of multimodality neoadjuvant therapy for esophageal cancer in the United States: assessment of 987 hospitals. *Ann Surg Oncol*. 2012;19:357–364.
178. Stein HJ, Feiht M, Brucher BL, et al. Early esophageal cancer: pattern of lymphatic spread and prognostic factors for long-term survival after surgical resection. *Ann Surg* 2005;242:566–573.
179. Dunbar KB, Spechler SJ. The risk of lymph-node metastases in patients with high-grade dysplasia or intramucosal carcinoma in Barrett's esophagus: a systematic review. *Am J Gastroenterol* 2012;107:850–862.
180. Rastogi A, Puli S, El-Serag HB, et al. Incidence of esophageal adenocarcinoma in patients with Barrett's esophagus and high-grade dysplasia: a meta-analysis. *Gastrointest Endosc* 2008;67:394–398.
182. Konda VJ, Ross AS, Ferguson MK. Is the risk of concomitant invasive esophageal cancer in high-grade dysplasia in Barrett's esophagus overestimated? *Clin Gastroenterol Hepatol* 2008;6:159–164.
186. Dar MS, Goldblum JR, Rice TW, et al. Can extent of high grade dysplasia in Barrett's oesophagus predict the presence of adenocarcinoma at oesophagectomy? *Gut* 2003;52:486–489.
187. Overholt BF, Lightdale CJ, Wang KK, et al. Photodynamic therapy with porfimer sodium for ablation of high-grade dysplasia in Barrett's esophagus: international, partially blinded, randomized phase III trial. *Gastrointest Endosc* 2005;62:488–498.
192. Shaheen NJ, Sharma P, Overholt BF, et al. Radiofrequency ablation in Barrett's esophagus and dysplasia. *N Engl J Med* 2009;360:2277–2288.
193. Ell C, May A, Pech O, et al. Curative endoscopic resection of early esophageal adenocarciomas (Barrett's cancer). *Gastrointest Endosc* 2007;65:3–10.
198. Chennat J, Konda V, Ross AS, et al. Complete Barrett's eradication endoscopic mucosal resection: an effective treatment modality for high-grade dysplasia and intramucosal carcinoma—an American single-center experience. *Am J Gastroenterol* 2009;104:2684–2692.
199. Bennett C, Vakil N, Bergman J, et al. Consensus statements for management of Barrett's dysplasia and early-stage esophageal adenocarcinoma, based on a Delphi process. *Gastroenterology* 2012;143:336–346.
204. Dunn DH, Johnson EM, Morphew JA, et al. Robot-assisted transhiatal esophagectomy: a 3-year single-center experience. *Dis Esophagus* 2013;26:159–166.
205. Luketich JD, Pennathur A, Awais O. Outcomes after minimally invasive esophagectomy: review of over 1000 patients. *Ann Surg* 2012;256:95–103.
206. Pennathur A, Farkas A, Krasinskas AM, et al. Esophagectomy for T1 esophageal cancer: outcomes in 100 patients and implications for endoscopic therapy. *Ann Thorac Surg* 2009;87:1048–1054.
208. Wu PC, Posner MC. The role of surgery in the management of oesophageal cancer. *Lancet Oncol* 2003;4:481–488.
209. Biere SS, van Berge Henegouwen MI, Maas KW, et al. Minimally invasive versus open oesophagectomy for patients with oesophageal cancer: a multicentre, open-label, randomised controlled trial. *Lancet* 2012;379:1887–1892.
215. Birkmeyer JD, Siewers AE, Finlayson EV, et al. Hospital volume and surgical mortality in the United tates. *N Engl J Med* 2002;346:1128–1137.
218. Wouters MW, Karin-Kos H, le Cessie S, et al. Centralization of esophageal cancer surgery: does it improve clinical outcomes? *Ann Surg Oncol* 2009;16:1789–1798.
219. Reames BN, Ghaferi AA, Birkmeyer JD, et al. Hospital Volume and Operative Mortality in the Modern Era. *Ann Surg* 2013 Dec 23 [Epub Ahead of Print].
220. Posner MC. Techniques of esophageal resection. In: Posner MC, Vokes EE, Weichselbaum RR, eds. *Cancer of the Upper Gastrointestinal Tract*. Hamilton, Ontario: BC Decker; 2002:1.
225. Orringer MB, Marshall B, Chang AC, et al. Two thousand transhiatal esophagectomies: changing trends, lessons learned. *Ann Surg* 2007;246:363–372.
232. McKeown KC. Total three-stage oesophagectomy for cancer of the oesophagus. *Br J Surg* 1976;63:259–262.
234. Bizekis C, Kent MS, Luketich JD, et al. Initial experience with minimally invasive Ivor Lewis esophagectomy. *Ann Thorac Surg* 2006;82:402–406.
240. Bosset JF, Gignoux M, Triboulet JP, et al. Chemoradiotherapy followed by surgery compared with surgery alone in squamous cell cancer of the esophagus. *N Engl J Med* 1997;337:161–167.
242. Hulscher JB, Tijssen JG, Obertop H, et al. Transthoracic versus transhiatal resection for carcinoma of the esophagus: a meta-analysis. *Ann Thorac Surg* 2001;72:306–313.
243. Boshier PR, Anderson O, Hanna GB. Transthoracic versus transhiatal esophagectomy for the treatment of esophagogastric cancer: a meta-analysis. *Ann Surg* 2011;254:894–906.
245. Chang AC, Ji J, Birkmeyer NJ, et al. Outcomes after transhiatal and transthoracic esophagectomy for cancer. *Ann Thorac Surg* 2008;85:424–429.
249. Hulscher JB, van Sandick JW, deBoer AG, et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. *N Engl J Med* 2002;347:1662–1669.
250. Omloo JM, Lagarde SM, Hulscher JB, et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the mid/distal esophagus: five-year survival of randomized clinical trial. *Ann Surg* 2007;246:992–1000.
252. Lerut T, Nafteux P, Moons J, et al. Three-field lymphadenectomy for carcinoma of the esophagus and gastroesophageal junction in 174 R0 resections: impact on staging, disease-free survival, and outcome: a plea for adaptation of TNM classification in upper-half esophageal carcinoma. *Ann Surg* 2004;240:962–972.
266. Cunningham D, Allum W, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006;355:11–20.
267. Ychou M, Boige V, Pignon JP, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNLCC and FFCF multicenter phase III trial. *J Clin Oncol* 2011;29:1715–1721.
268. Schuhmacher C, Gretschel S, Lordick F, et al. Neoadjuvant chemotherapy compared with surgery alone for locally advanced cancer of the stomach and cardia: European Organization for Research and Treatment of Cancer randomized Trial 40954. *J Clin Oncol* 2010;28:5210–5218.
269. Boonstra JJ, Kok TC, Wijnjoven BPL, et al. Chemotherapy followed by surgery versus surgery alone in patients with resectable oesophageal squamous cell carcinoma: long-term results of a randomized trial. *BMC Cancer* 2011;11:181.
270. Thirion PG, Michiels S, LeMaitre A, et al. Individual patient data based meta analysis assessing preoperative chemotherapy in resectable oesophageal cancer. *J Clin Oncol* 2007;25:4512.
273. Teniere P, Hay JM, Fingerhut A, et al. Postoperative radiation therapy does not increase survival after curative resection for squamous cell carcinoma of the middle and lower esophagus as shown by a multicenter controlled trial. French University Association for Surgical Research. *Surg Gynecol Obstet* 1991;173:123.
280. Herskovic A, Martz K, Al-Sarraf M, et al. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. *N Engl J Med* 1992;326:1593–1598.
281. Minsky B, Pajak T, Ginsberg RJ, et al. INT 0123 (Radiation Therapy Oncology Group 94–05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. *J Clin Oncol* 2002;20:1167–1174.
284. Forastiere A, Orringer MB, Perez-Tamayo C, et al. Preoperative chemoradiation followed by transhiatal esophagectomy for carcinoma of the esophagus: final report. *J Clin Oncol* 1993;11:1118–1123.
301. Meredith K, Weber J, Turaga K, et al. Pathologic response after neoadjuvant therapy is the major determinant of survival in patients with esophageal cancer. *Ann Surg Oncol* 2010;17:1159–1167.
302. Leichman LP, Goldman BH, Bohanes PO, et al. S0356: A phase II clinical and a prospective molecular trial with oxaliplatin, fluorouracil, and external-beam radiation therapy before surgery for patients with esophageal adenocarcinoma. *J Clin Oncol* 2011;29:4555–4560.
317. Van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 2012;366:2074–2084.
318. Sarkaria IS, Rizk NP, Bains MS, et al. Post-treatment endoscopic biopsy is a poor predictor of pathologic response in patients undergoing chemoradiation therapy for esophageal cancer. *Ann Surg* 2009;249:764–767.
319. Chedella NKS, Suzuki A, Xiao L, et al. Association between clinical complete response and pathological complete response after preoperative chemoradiation in patients with gastroesophageal cancer: analysis in a large cohort. *Ann Oncol* 2013;24:1262.
320. Yang Q, Cleary KR, Yao JC, et al. Significance of post-chemoradiation biopsy in predicting residual esophageal carcinoma in the surgical specimen. *Dis Esophagus* 2004;14:38–43.
326. Fields RC, Strong VE, Gonen M, et al. Recurrence and survival after pathologic complete response to preoperative therapy followed by surgery for gastric or gastroesophageal adenocarcinoma. *Br J Cancer* 2011;104:1840–1847.
327. Downey RJ, Akhurst T, Ilson D, et al. Whole body 18FDG-PET and the response of esophageal cancer to induction therapy: results of a prospective trial. *J Clin Oncol* 2003;21:428–432.

۰۲۱-۶۶۱۹۸۵۱۴ www.myuptodate.com tahir99 - UnitedVRG دریافت آخرین نسخه آپتودیت آفلاین

328. Flamen P, Van Cutsem E, Lerut A, et al. Positron emission tomography for assessment of the response to induction radiochemotherapy in locally advanced oesophageal cancer. *Ann Oncol* 2002;13:361–368.
329. Vallböhmer D, Holscher AH, Dietleiin M, et al. [18F] fluorodeoxyglucose-positron emission tomography for the assessment of histologic response and prognosis after completion of neoadjuvant chemoradiation in esophageal cancer. *Ann Surg* 2009;250:888–894.
330. Klayton T, Li T, Yu JQ, et al. The role of qualitative and quantitative analysis of F18-FDG positron emission tomography in predicting pathologic response following chemoradiotherapy in patients with esophageal carcinoma. *J Gastrointest Surg* 2012;43:612–618.
332. Monjazeb AM, Riedlinger G, Aklilu M, et al. Outcomes of patients with esophageal cancer staged with [18F] fluorodeoxyglucose positron emission tomography (FDG-PET): can postradiochemotherapy FDG-PED predict the utility of resection? *J Clin Oncol* 2010;28:4714–4721.
334. McCurdy M, McAleer MF, Wei W, et al. Induction and concurrent taxanes enhance both the pulmonary metabolic response and the radiation pneumonitis response in patients with esophagus cancer. *Int J Radiat Oncol Biol Phys* 2010;76:816–823.
337. Kleinberg L, Powell ME, Forastiere AA, et al. Survival outcome of E1201: an Eastern Cooperative Oncology Group randomized phase II trial of neoadjuvant preoperative paclitaxel/cisplatin/radiotherapy or irinotecan/cisplatin/radiotherapy in endoscopy with ultrasound stage esophageal adenocarcinoma. *J Clin Oncol* 2008;26:4532.
338. Kleinberg LR, Eapen S, Hamilton S, et al. E1201: an Eastern Cooperative Oncology Group (ECOG) randomized phase II trial to measure response rate and toxicity of preoperative combined modality paclitaxel/cisplatin/RT or irinotecan/cisplatin/RT in adenocarcinoma of the esophagus. *Int J Rad Oncol Biol Phys* 2006;66:s173.
339. Walsh TN, Noonan N, Hollywood D, et al. A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. *N Engl J Med* 1996;335:462–467.
341. Burmeister BH, Smithers BM, Gebski V, et al. Surgery alone versus chemoradiotherapy followed by surgery for resectable cancer of the oesophagus: a randomised controlled phase III trial. *Lancet Oncol* 2005;6:659–668.
342. Tepper J, Krasna MJ, Niedzwiecki D, et al. Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781. *J Clin Oncol* 2008;26:1086–1092.
344. Stahl M, Walz MK, Stuschke M, et al. Phase III comparison of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced adenocarcinoma of the esophagogastric junction. *J Clin Oncol* 2009;27:851–856.
345. Le Prise E, Etienne PL, Meunier B, et al. A randomized study of chemotherapy, radiation therapy, and surgery versus surgery for localized squamous cell carcinoma of the esophagus. *Cancer* 1994;73:1779–1784.
346. Kaklamanos IG, Walker GR, Ferry K, et al. Neoadjuvant treatment for resectable cancer of the esophagus and gastroesophageal junction: a meta-analysis of randomized clinical trials. *Ann Surg Oncol* 2003;10:754–761.
347. Sjoquist KM, Burmeister BH, Smithers BM, et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. *Lancet Oncol* 2011;12:681–692.
349. Crosby T, Hurt CN, Falk S, et al. Chemoradiotherapy with or without cetuximab in patients with oesophageal cancer (SCOPE-1): a multicenter, phase 2/3 randomized trial. *Lancet Oncol* 2013;14:627–637.
360. MacDonald J, Benedetti J, Smalley S, et al. Chemoradiation of resected gastric cancer: a 10-year follow-up of the phase III trial INT 0116 (SWOG 9008). *Proc Am Soc Clin Oncol* 2009;27:205s.
361. Gordon MA, Gundacker HM, Benedetti J, et al. Assessment of HER2 gene amplification in adenocarcinomas of the stomach or gastroesophageal junction in the INT-0116/SWOG9008 clinical trial. *Ann Oncol* 2013;24:1754–1761.
363. al-Sarraf M, Martz K, Herskovic A, et al. Superiority of chemo-radiotherapy (CT-RT) vs radiotherapy (RT) in patients with esophageal cancer. Final report of an Intergroup randomized and confirmed study. *Proc Am Soc Clin Oncol* 1996;15:abst 206.
364. Suntharalingam M, Moughhan J, Cola LR, et al. Outcome results of the 1996–1999 patterns of care survey of the national practice for patients receiving radiation therapy for carcinoma of the esophagus. *J Clin Oncol* 2005;23:2325–2331.
372. al-Sarraf M, Martz K, Herskovic A, et al. Progress report of combined chemoradiotherapy versus radiotherapy alone in patients with esophageal cancer: an Intergroup study. *J Clin Oncol* 1997;15:277–284.
376. Wong RK, Malthaner RA, Zuraw L, et al. Combined modality radiotherapy and chemotherapy in nonsurgical management of localized carcinoma of the esophagus: a practice guideline. *Int J Radiat Oncol Biol Phys* 2003;55:930–942.
378. Yu J, Ren R, Sun X, et al. A randomized clinical study of surgery versus radiotherapy in the treatment of resectable esophageal cancer. *Proc Am Soc Clin Oncol* 2006;24:181s.
379. Chiu PWY, Chan ACW, Leung SF, et al. Multicenter prospective randomized trial comparing standard esophagectomy with chemoradiotherapy for treatment of squamous esophageal cancer: early results from the Chinese University Research Group for Esophageal Cancer (CURE). *J Gastrointest Surg* 2005;9:794.
382. Crehange G, Maingon P, Peignaux K, et al. Phase III trial of protracted compared with split-course chemoradiation for esophageal cancer: Federation Francophone de Cancerologie Digestive 9102. *J Clin Oncol* 2007;25:4895–4901.
385. Swisher SG, Hofsetter W, Wu TT, et al. Proposed revision of the esophageal cancer staging system to accommodate pathologic response (pP) following preoperative chemoradiation (CRT). *Ann Surg* 2005;241:810–817.
386. Swisher SG, Winter KA, Komaki RU, et al. A phase II study of a paclitaxel-based chemoradiation regimen with selective surgical salvage for resectable locoregionally advanced esophageal cancer: initial reporting of RTOG 0246. *Int J Radiat Oncol Biol Phys* 2012;82:1967–1972.
395. Skinner HD, Xu E, Lee JH, et al. A validated miRNA expression profile for response to neoadjuvant therapy in esophageal cancer. *Proc ASCO* 2013;31:4078(abstr).
398. Brucher BL, Becker K, Lordick F, et al. The clinical impact of histopathologic response assessment by residual tumor cell quantification in esophageal squamous cell carcinomas. *Cancer* 2006;106:2119–2127.
399. McLoughlin J, Melis M, Siegel E, et al. Are patients with esophageal cancer who become PET negative after neoadjuvant chemoradiation free of cancer. *J Am Coll Surg* 2008;206:879–886.
412. Homs MY, Essink-Bot ML, Borsboom GJ, et al. Quality of life after palliative treatment for oesophageal carcinoma—a prospective comparison between stent placement and single dose chemotherapy. *Eur J Cancer* 2004;40:1862–1871.
418. Ishikawa H, Nonaka T, Sakurai H, et al. Usefulness of intraluminal brachytherapy combined with external beam radiation therapy for submucosal esophageal cancer: long-term follow-up results. *Int J Rad Oncol Biol Phys* 2010;76:452–459.
419. Gaspar LE, Qian C, Kocha WI, et al. A phase I/II study of external beam radiation, brachytherapy and concurrent chemotherapy in localized cancer of the esophagus (RTOG 92–07): preliminary toxicity report. *Int J Radiat Oncol Biol Phys* 1997;37:593–599.
421. Gaspar LE, Nag S. Herskovic A, et al. American Brachytherapy Society (ABS) consensus guidelines for brachytherapy of esophageal cancer. *Int J Radiat Oncol Biol Phys* 1997;38:127–132.
428. Kole TP, Aghayere O, Kwah J, et al. Comparison of heart and coronary artery doses associated with intensity-modulated radiotherapy versus three-dimensional conformal radiotherapy for distal esophageal cancer. *Int J Radiat Oncol Biol Phys* 2012;83:1580–1586.
429. Yin L, Wu H, Gong J, et al. Volumetric-modulated arc therapy vs. c-IMRT in esophageal cancer: a treatment planning comparison. *World J Gastroenterol* 2012;18:5266–5275.
436. Lin SH, Wang L, Myles B, et al. Propensity score-based comparison of long-term outcomes with 3-dimensional conformal radiotherapy vs. intensity-modulated radiotherapy for esophageal cancer. *Int J Radiat Oncol Biol Phys* 2012;84:1078–1085.
440. Nishimura Y, Nagata K, Katano S, et al. Severe complications in advanced esophageal cancer treated with radiotherapy after intubation of esophageal stents: a questionnaire survey of the Japanese Society for Esophageal Diseases. *Int J Radiat Oncol Biol Phys* 2003;56:1327.
450. Coia LR, Soffen EM, Schultheiss TE, et al. Swallowing function in patients with esophageal cancer treated with concurrent radiation and chemotherapy. *Cancer* 1993;71:281–286.
452. Sur M, Sur R, Cooper K, et al. Morphologic alterations in esophageal squamous cell carcinoma after preoperative high dose rate intraluminal brachytherapy. *Cancer* 1996;77:2200–2205.
455. Minsky BD. The adjuvant treatment of esophageal cancer. *Sem Radiat Oncol* 1994;4:165–169.
462. Lin SH, Komaki R, Liao Z, et al. Proton beam therapy and concurrent chemotherapy for esophageal cancer. *Int J Radiat Oncol Biol Phys* 2012;83:e345–e351.
470. Konski A, Li T, Christensen M, et al. Symptomatic cardiac toxicity is predicted by dosimetric and patient factors rather than changes in 18F-FDG PET determination of myocardial activity after chemoradiotherapy for esophageal cancer. *Radiother Oncol* 2012;104:72–77.
471. Rueth NM, Shaw D, D'Cunha J, et al. Esophageal stenting and radiotherapy: a multimodal approach for the palliation of symptomatic malignant dysphagia. *Ann Surg Oncol* 2012;19:4223–4228.
483. Bleiberg H, Conroy T, Paillot B, et al. Randomised phase II study of cisplatin and 5-fluorouracil (5-FU) versus cisplatin alone in advanced squamous cell oesophageal cancer. *Eur J Cancer* 1997;33:1216–1220.
517. Webb A, Cunningham D, Scarffe JH, et al. Randomized trial comparing epirubicin, cisplatin, and fluorouracil versus fluorouracil, doxorubicin, and methotrexate in advanced esophagogastric cancer. *J Clin Oncol* 1997;15:261–267.
518. Ross P, Nicholson M, Cunningham D, et al. Prospective randomized trial comparing mitomycin, cisplatin, and protracted venous-infusion fluorouracil (PVI 5-FU) with epirubicin, cisplatin, and PVI 5-FU in advanced esophagogastric cancer. *J Clin Oncol* 2002;20:1996.
520. Cunningham D, Starling N, Rao S, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. *N Engl J Med* 2008;358:36–46.
521. Al-Batran S, Hartmann J, Probst S, et al. Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: a study of the Arbeitsgemeinschaft Internistische Onkologie. *J Clin Oncol* 2008;26:1435–1442.

۰۲۱-۶۶۱۹۸۵۱۴ www.myuptodate.com دریافت آخرین نسخه آپتودیت آفلاین

522. Kang YK, Kang KW, Shin DB, et al. Capecitabine/cisplatin versus 5-fluorouracil/cisplatin as first-line therapy in patients with advanced gastric cancer: a randomized phase III noninferiority trial. *Ann Oncol* 2009;20:666–673.
523. Koizumi W, Narahara H, Hara T, et al. S-1 plus cisplatin versus S-1 alone for first line treatment of advanced gastric cancer (SPIRITS Trial): a phase III trial. *Lancet Oncol* 2008;9:215–221.
524. Ajani JR, Correa A, Walsh G, et al. Multicenter phase III comparison of cisplatin/S-1 with cisplatin/infusional fluorouracil in advanced gastric or gastroesophageal adenocarcinoma study: the FLAGS Trial. *J Clin Oncol* 2010;28:1547–1553.
525. Van Cutsem E, Moiseyenko VM, Tjulandin S, et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 study group. *J Clin Oncol* 2006;24:4991–4997.
526. Al-Batran SE, Pauligk C, Homann N, et al. The feasibility of triple-drug chemotherapy combination in older adult patients with esophagogastric cancer: a randomized trial of the Abreitsgemeinschaft Internistische Onkologie (FLOT65+). *Eur J Cancer* 2013;49:835–842.
540. Ilson DH, Saltz L, Enzinger P, et al. Phase II trial of weekly irinotecan plus cisplatin in advanced esophageal cancer. *J Clin Oncol* 1999;17:3270–3275.
541. Ajani JA, Baker J, Pisters PW, et al. CPT-11 plus cisplatin in patients with advanced, untreated gastric or gastroesophageal junction carcinoma: results of a phase II study. *Cancer* 2002;94:641–646.
542. Enzinger PC, Ryan D, Clark J, et al. Weekly docetaxel, cisplatin, and irinotecan (TPC): results of a multicenter phase II trial in patients with metastatic esophagogastric cancer. *Ann Oncol* 2009;20:475–480.
543. Enzinger PC, Burtness BA, Hollis DR, et al. CALGB 80403 / ECOG 1206: Randomized phase II study of standard chemotherapy plus cetuximab for metastatic esophageal cancer. *J Clin Oncol* 2010;28:15S.
549. Dank M, Zaluski J, Barone C, et al. Randomized phase III study comparing irinotecan combined with 5-fluorouracil and folinic acid to cisplatin combined with 5-fluorouracil in chemotherapy naive patients with advanced adenocarcinoma of the stomach or esophagogastric junction. *Ann Oncol* 2008;19:1450–1457.
552. Bang YJ, Van Cutsem E, Fevereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastroesophageal junction cancer (ToGA): a phase 3, open-label, randomized controlled trial. *Lancet* 2010;376:687–697.
553. Yoon HH, Shi Q, Sukov WR, et al. Association of HER2/ErbB2 expression and gene amplification with pathologic features and prognosis in esophageal adenocarcinomas. *Clin Cancer Res* 2012;18:546–554.
557. Dutton SJ, Blazeby JM, Petty RD, et al. Patient-reported outcomes from a phase III muticenter, randomized double-blind, placebo-controlled trial of gefitinib versus placebo in esophageal cancer progressing after chemotherapy: Cancer Oesophagus Gefitinib (COG). *J Clin Oncol* 2012;30:S34.
558. Pinto C, DiFabio F, Siena S, et al. Phase II study of cetuximab in combination with FOLFIRI in patients with untreated advanced gastric or gastroesophageal junction adenocarcinoma. *Ann Oncol* 2006;18:510–517.
559. Lorenzen S, Schuster T, Porschen R, et al. Cetuximab plus cisplatin 5-fluorouracil versus cisplatin 5-fluorouracil alone in first line metastatic squamous cell carcinoma of the esophagus: a randomized phase II trial. *Ann Oncol* 2009;20:1667–1673.
560. Lordick F, Luber B, Lorenzen S, et al. Cetuximab plus oxaliplatin/leucovorin/5-fluorouracil in first line metastatic gastric cancer: a phase II study. *Br J Cancer* 2010;102:500–505.
561. Enzinger PC, Burtness BA, Hollis DR, et al. CALGB 80403/ECOG 1206: Randomized phase II study of standard chemotherapy plus cetuximab for metastatic esophageal cancer. *J Clin Oncol* 2010;28:15S.
562. Waddell T, Cunningham D, Gonzalez D, et al. Epirubicin, oxaliplatin, and capecitabine with or without panitumumab for patients with previously untreated esophagogastric cancer (REAL-3): a randomized, open-label phase 3 trial. *Lancet Oncol* 2013;14:481.
563. Lordick F, Kang YK, Chung HC, et al. Capecitabine and cisplatin with or without cetuximab for patients with previously untreated gastric cancer (EXPAND): a randomized, open-label phase 3 trial. *Lancet Oncol* 2013;14:490–499.
564. Lorenzen S, Schuster T, Porschen R, et al. Cetuximab plus cisplatin-5-fluorouracil versus cisplatin-5-fluorouracil alone in first-line metastatic squamous cell carcinoma of the esophagus: a randomized phase II study of the Arbeitsgemeinschaft Internistische Onkologie. *Ann Oncol* 2009;20:1667–1673.
566. Ohtsu A, Shah MA, van Cutsem E, et al. Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: a randomized, double-blind, placebo-controlled phase III study. *J Clin Oncol* 2011;29:3968–3976.
567. Fuchs CS, Tomasek J, Yang CJ, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-esophageal junction adenocarcinoma (REGARD): an international, randomized, multicenter, placebo-controlled, phase 3 trial. *Lancet* 2014;383:31–39.
568. Ohtsu A, Ajani JA, Bai YX, et al. Everolimus in previously treated, advanced gastric cancer: results of the randomized, double-blind, phase III GRANITE-1 Study. *J Clin Oncol* 2013;31:3935–3943.

۰۲۱-۶۶۱۹۸۵۱۴ www.myuptodate.com tahir99 - UnitedVRG دریافت آخرین نسخه آپتودیت آفلاین